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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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SECTION ON MICROBIOLOGY

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CONTENTS

Topectomy—Surgical Indications and Results 335
J. Lawrence Pool, Robert G. Heath and John J. Weber

Therapy of Asthma with Reference to Its Psychodynamic Pharmacology 345
Harold A. Abramson

Medicine Under Mussolini 364
Mario Volterra

Section on Microbiology

Chemical Aspects of Some of the Newer Insecticides, *H. L. Haller* 374

The Major Toxic Actions of Insecticides, *Arnold J. Lehman* 382

Recent Advances in Medical and Veterinary Entomology, *E. F. Knipling* 388

Library Notes:

Recent Accessions to the Library 397

Communication to the Editor 400

Announcement 400

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TOPECTOMY: SURGICAL INDICATIONS AND RESULTS*

J. Lawrence Pool, Robert G. Heath, and
John J. Weber

Topectomy (from "topos," place; "ektome," a cutting-out)[1] is an operation consisting of limited bilateral ablation of cortex from the frontal lobes for the treatment of mental illness. While cortical ablation[2] or frontal gyrectomy[3] are also acceptable terms, topectomy is more concise and perhaps more accurate because it signifies a topical resection of cortex according to the approximate limits of Brodmann's areas or portions thereof, whereas frontal gyrectomy suggests removal according to specific frontal gyri.

Topectomy has evolved after considerable trial into a fairly standard type of operation involving bilateral removal of the rostromedial portion of each frontal lobe, believed to represent (approximately) the medial portions of areas 9 and 10 of Brodmann.[4] Cortical removals are begun 2.5 cm. in front of the coronal suture when it crosses the midline, and thence extend 5.5 cm. anteriorally; 3.5 cm. laterally; and 1.9 to 2.0 cm. in depth. Each excision is thus carried to the depths of the gray matter but not into the underlying white matter as in lobotomy. Hence topectomy spares a great deal more of both the gray and the

* Presented March 3, 1949 before the Stated Meeting of The New York Academy of Medicine. From the Service of Neurological Surgery, Neurological Institute, New York.

white matter of each frontal lobe than does lobotomy, and is accordingly in this respect a more conservative type of operation.

General Indications: Any attempt at surgical relief of mental illness is, in general, indicated only when other appropriate types of therapy have been tried and have failed. In all but two of our cases, insulin or electrical shock treatment as well as psychotherapy had been used without lasting success before operation was carried out.

Specific Indications: Specific indications for topectomy are essentially the same as for prefrontal lobotomy, with one notable exception: Topectomy, being less radical as to the amount of brain tissue sacrificed, is in general not indicated for the purpose of rendering a violently assaultive psychotic patient into a tractable but perhaps apathetic automaton. (A more detailed description of the indications for topectomy is now in preparation.)

Type of Patient: As a result of analyzing post-topectomy effects in the chronic, deteriorated "back" ward schizophrenic as well as those in the more acute, less deteriorated group, it appears that the best results may be expected in those schizophrenic patients who still manifest at least some evidence of "drive" and some indication of emotional reaction or affect. Although there are exceptions our results indicate in general that the patient's age at the onset of illness, previous response to shock treatment, duration of illness, and perhaps the intellectual level are important prognostic considerations. Thus schizophrenic patients over 45 years of age usually fail to profit by operation, especially if symptoms have been prominent for many years and appeared early in life. Another extremely important factor in selecting candidates for topectomy, as it is for lobotomy, is the social background. We have found that a sympathetic and helpful climate in the patient's home is virtually imperative if a good result is to be maintained. It is, of course, also most important that follow-up psychotherapy be available if the initial gain following operation is to be extended. The majority of patients referred for topectomy have been schizophrenic but this group is not the only one in which improvement occurs. Other categories of mental disturbances for which topectomy is indicated are obsessive-compulsive neurosis and depressions that do not respond to the usual types of treatment. Results have been best in the obsessive-compulsive group and the affective disorders including involutional depression, agitated depression and the depressed phase of the manic-depressive

psychosis. Poor results were obtained in reactive depressions associated with Parkinson's disease; and two psychopaths responded poorly although there are theoretical reasons to expect a favorable response in some members of this group. Good results without personality changes have been reported following a less radical bilateral topectomy for the relief of intractable pain, but the authors have had no experience with this use of topectomy.

Incidental Observations

Pathology: Certain interesting and perhaps valuable observations have been made during the course of topectomy operations owing to the rather generous exposure of the brain they require. First and foremost is the fact that my associates and I, and other neurosurgeons with experience in this field, have noted that a large percentage of psychotic patients appear to have a grossly abnormal brain both as to appearance and consistency. Approximately two-thirds of our patients clearly seemed to have gross abnormalities of the brain at operation:—23 of the 36 schizophrenics, and 14 of the 18 patients in the other groups. These changes were characterized by definite reduction in the size of the cerebral gyri, a marked increase of the subarachnoid fluid, and a thickened, hard or rubbery consistency of the underlying brain. In some cases the cortex was yellowish; in others, there seemed to be an excess of small cortical blood vessels, while in many the arachnoid membrane was not transparent as in the normal state, but milky, translucent or spotted. Finally, in many cases the cingulate gyri were found to be densely adherent by arachnoidal adhesions, as if glued together. In contrast, the brains of the remaining third of our patients thus inspected seemed entirely or almost normal, particularly those of the obsessive-compulsive group. It thus seems clear that many psychotic patients harbor a grossly pathological looking brain. The significance of this observation is not apparent, especially as microscopic analysis fails to reveal very much beyond scattered shrunken or distorted and deeply staining nerve cells. Specific changes in the oligodendroglial cells were not demonstrable.[5] Perhaps the observed gross changes at operation indicate disturbed cerebral metabolism, as yet unexplained, along the lines suggested by Stockings.[6] Certainly the pathological changes cannot be ascribed to shock therapy as they were present in several patients who had not had shock treatment, and conversely were not found in

some patients who had undergone extensive shock treatment. Nor is age necessarily a factor as two schizophrenic patients were quite young and yet showed advanced pathological changes, while several patients in the fifth or sixth decades presented quite normal looking brains.

As to a correlation between cortical atrophy and postoperative results:—Of those patients with a moderate degree of cerebral atrophy, approximately half showed postoperative improvement while the other half failed to improve after topectomy. While a few with advanced atrophy improved a great deal and a few with a normal looking brain failed to improve, in general those with advanced atrophy failed to improve, while those with normal looking brains seemed as a group most apt to improve.

Autonomic Nervous System

Effects upon the autonomic nervous system often become manifest following topectomy as they may after lobotomy. Many patients tend to gain weight, perhaps in part because their anxiety has been lessened, while a few that do not improve may lose weight. Two hypertensive patients have maintained a marked reduction in their blood pressure after topectomy, one for two years. Others may show temporary improvement in the peripheral circulation; while after some of the early area 9 (Brodmann) ablations, retention of urine occurred for some days that may represent a "release" effect upon the bladder complex of the cerebral cortex. Finally, it may be appropriate to mention the effects of stimulation of the cingulate gyri in its rostral portion, which in the experimental animal has been shown to elicit profound alterations in the heart rate, blood pressure and respiratory rate. It can now be said that the same phenomena follow electrical excitation and even mechanical stimulation of the rostral cingulate cortex in man.[7] This is an observation that may sometime prove of value in the treatment of diseases referable to the autonomic system.

Amount of Cortex

Before turning to the actual results of topectomy the amount of cortex sacrificed by the operation should be considered, for careful analysis of this factor suggests two things: first, that an adequate amount of cortex must be removed if a good result is to be obtained; and secondly, that in some cases (particularly the advanced chronic or

deteriorated schizophrenic), no matter how much cortex is removed there will be no significant improvement, at least as far as social rehabilitation is concerned. These two views suggest as a corollary that if an adequate amount of cerebral tissue is removed (and the amount can be quite well judged by measurements and weights of the ablated tissue) there is as a rule no value in removing further cortex if the psychotic condition fails to improve.

Removal of about 30 grams for *each* frontal lobe seems to be the average effective amount. Somewhat more than this has had to be removed in a few chronic schizophrenics at a second operation before improvement took place, while less than this amount has proved effective in depressed or obsessive states.

In a word, topectomy has proved an excellent opportunity for arriving at some idea of whether or not a quantitative factor is important in frontal lobe operations of this kind. It is our feeling that a quantitative factor is important. However, we also feel that the qualitative or anatomical factor is important, on the basis of this and other work of a similar nature and certain laboratory data. Perhaps one reason that ablation of cortex from the region of what we believe represents the rostromedial portions of areas 9 and 10 of Brodmann, is that this region is an important station for thalamocortical projections (especially those of the dorso-median nuclei of the thalamus).[8, 9, 10] Interruption of this circuit seems to be a vital factor in reducing the anxiety underlying psychoses and other mental states, and of course this reduction of anxiety is one of the chief aims of psychosurgery.

Results of Topectomy—1. *Postoperative course:* The postoperative course is generally marked by immediate signs of improvement if the eventual outcome is to be successful. About 24 hours after operation, however, there may be an accentuation of psychotic manifestations or abnormal behavior, particularly in expressions of hostility and resentment. Hallucinations may or may not disappear at this time. Four or five days later improvement begins to be apparent, and from then on there is usually a steadily improving course in the favorable cases. For a period sometimes lasting weeks or months, there may be some degree of euphoria or dulling of mental acuity and "drive," although this is not invariably so. Such a picture usually appears in the schizophrenics and appears to be more related to the pre-existing psychopathology than to the operation. Fatigability is often slow to disappear, while

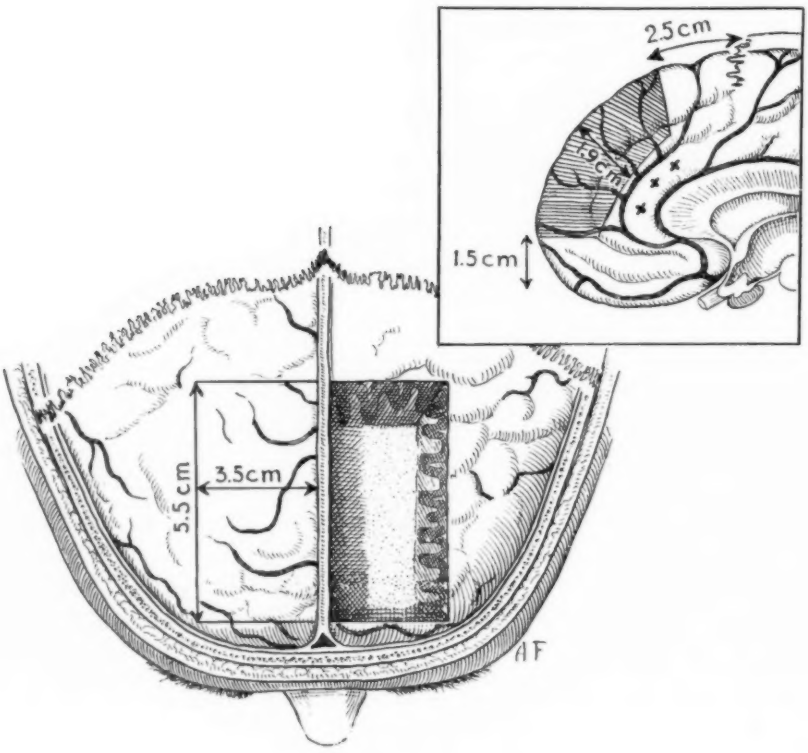

FIGURE 1.—Diagram showing approximate site and extent of cortical excision in topectomy. Excision is greatly simplified if the branches of the anterior cerebral arteries on the medial surface of the frontal lobes (shaded area in inset) are ligated with silver clips before attempting ablation. Large venous channels can then be secured between silver clips while smaller vessels may be lightly cauterized with the electrocautery. (Silk ligatures are no longer used). The cortex is then cleanly incised with a No. 11 scalpel all around the margins of the shaded area and removed as one block. Care is taken that the blade goes no deeper than 1.9 cm. (the average depth of the gray matter). Before closure, the margins of the cavity are made even with a small calibre suction tip and meticulous hemostasis is secured. The dura is closed in water-tight fashion, the bone flap anchored in place, and the anterior burr holes covered with small tantalum discs. A drain is seldom necessary.

NOTE: Crosses (X) on rostral aspect of cingulate gyrus indicate regions yielding autonomic responses on electrical or mechanical excitation.[7]

technical ability is seldom affected after topectomy, so that musicians and painters, for example, usually resume their special work within two weeks after topectomy.

2. *Incontinence:* About one-third of our patients are temporarily incontinent of urine for 2 to 23 days and a few have been doubly incontinent, but only temporarily. None have been permanently incontinent so far as we know.

3. *Mortality:* There have been no deaths in this series of 54 consecutive topectomies performed during the last 2½ years, all of whom have been followed for at least six months. A total of 92 topectomy operations has now been done by one of the authors (J.L.P.) including 6 re-operations, with no operative fatalities, and in an additional 25 cases done by other neuro-surgeons, only one fatality has been reported. The overall mortality rate is thus less than 1 per cent, which compares favorably with the postlobotomy mortality rate with ranges from 1.5 per cent[11] to 6 per cent.[12]

4. *Convulsive seizures and electro-encephalogram* (*EEG*): Five of these 54 patients have had one or more postoperative convulsive seizures; that is, 10 per cent (Lobotomy: 7-11 per cent). All, however, are controlled by proper medication. In 4 the brain looked grossly abnormal at operation, but in one it did not. All of those who developed seizures and who had an EEG, showed abnormal activity in the frontal region bilaterally. One other patient had spiking in the prefrontal leads but did not have seizures, possibly because of precautionary anti-convulsant medication. Almost all other patients who had an EEG showed some abnormality in the prefrontal and often the temporal leads for 3-4 weeks, and occasionally longer, after operation. However, in most cases tested 6 months or more after topectomy, the EEG was reported as within normal limits. This observation is in keeping with the fact that so far none of our patients has developed seizures if they had been free of this complication for six months after operation. It may be added that in all our cases except one the pre-operative EEG was normal; and that anti-convulsant medication was never given unless indicated.

In the above 6 cases, seizures occurred regardless of whether the cortical ablation had been done with silk ligatures (2 cases), without ligatures (2 cases) or by the sub-pial technique (1 case).

5. *Other postoperative complications:* Two cases in this series were

TABLE I

Results are tabulated according to diagnosis and degree of improvement in 54 patients operated upon (topectomy) from October 1946 to September 1948. Marked improvement is rated as 4; moderate as 3; no improvement as zero; etc. This system of scoring, which takes into account the postoperative psychiatric status together with the degree of social rehabilitation, will be described in detail together with full case histories, in a subsequent communication now in preparation.

Diagnosis	*Degree of Improvement—3-1-49*					
	4	*3*	*2*	*1*	*0*	TOTAL
Schizophrenia (all types)	7	8	5	2	14	36
Manic-Depressive—Depressed	2					2
Manic-Depressive—Manic					1	1
Involutional Depression	2		1	2		5
Agitated Depression		1	2			3
Reactive Depression — Parkinsonism					2	2
Obsessive-Compulsive—Neurosis	3					3
Psychopath			1			1
Schizoid Psychopath				1		1
TOTAL	14	9	9	5	17	54

re-operated upon within three days after operation because of an extradural hematoma. Both had a very vascular dura and both made a rapid and completely non-eventful recovery. Another patient developed signs of peripheral neuritis, apparently due to avitaminosis secondary to deficiency in diet prior to operation. This rapidly improved with a high vitamin diet.

6. *Tabulation of results:* This series of 54 patients represents all cases on whom a topectomy was performed with cortical ablation from what was believed grossly to represent the approximate region of Brodmann's areas 9 and 10. In the bulk of these cases sub-total ablation of areas 9 and 10 together was done. The group includes an almost equal share of patients presumed to have had a reasonably good prognosis and those who were obviously deteriorated. Various categories were included with the idea of helping some patients who could not find help otherwise. It is to be hoped in the future, however, that as a result of this evaluation cases will be more carefully selected. (The bulk of the schizophrenic group, it should be stated, were of the paranoid type. Of three catatonic patients in the schizophrenic group, two made a significant improve-

ment). When improvement occurred in any of these groups it was usually apparent within three months. There was, however, one exception where improvement took place six months after operation. Only two relapses have so far occurred in any of the patients who had showed a reasonable degree of initial improvement, and these occurred 8 and 16 months after operation. With two possible exceptions we do not think any of our patients have been rendered the worse for their operations.

As for the results, they compare favorably with most of the published data on lobotomy, as is shown in Table I based on a strict and conservative evaluation of our cases. Thus we have obtained approximately 20 per cent good results in our schizophrenic cases while Poppen also reports 20 per cent *good* results in this type of patient following prefrontal lobotomy.[13] Another 20 per cent of our cases are significantly improved, so that they are at home and capable of housework, etc. but are not capable of earning their living. Those who are improved but still remain in an institution or even at home but who require care, are listed with our poor results; that is, with those cases who showed no improvement.

Of our best cases, their families say that they are the same as they were before their illness began. Those who worked are back at work, one as an accountant, another as a business man and others as secretaries, writers and housewives.

Summary

1. The operation known as topectomy is described as bilateral ablation of cortex from the rostro-medial portion of each frontal lobe, believed to be portions of Brodmann's areas 9 and 10.

2. The selection of patients is discussed, and it is urged that in the future the selection of cases for psychosurgery be more carefully carried out. The obsessive-compulsive and certain forms of depression profit most by topectomy. The deteriorated and deeply regressed schizophrenic and the psychopath apparently profit the least. Some manic-depressives in the depressed state may do very well.

3. The postoperative results in mentally disturbed patients are tabulated. Our results compare favorably with lobotomy results, and in this regard it may be said that we have had few of the profound and permanent personality disturbances that may follow prefrontal lobotomy.

4. Postoperative complications include temporary but not perma-

nent incontinence in about ⅓ of our cases; a 10 per cent incidence of seizures, all controlled by appropriate medication; two cases with post-operative hematoma, both successfully treated; and one case with peripheral neuritis, improved by appropriate treatment. The operative mortality rate has been zero.

5. It is currently our feeling that benefits from brain surgery in the mentally and emotionally sick may be attributed to two factors: one—quantitative, and the other qualitative or anatomical.

6. The electro-encephalogram has usually shown changes for a few weeks after topectomy, as it may after lobotomy, but in most instances shows no abnormalities six months after topectomy except in cases developing seizures.

7. Autonomic effects referable to the frontal lobes in man are briefly discussed, particularly as to stimulation of the rostral cingulate cortex.

8. Attention is directed to the impression that approximately two-thirds of our patients seemed clearly to have grossly pathological brains, although microscopic analysis failed to corroborate this impression. This suggests the urgent need for other types of study and analysis of the brains of psychotic patients, as a clue to the possibility of organic factors associated with certain mental diseases.

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THERAPY OF ASTHMA WITH REFERENCE TO ITS PSYCHODYNAMIC PHARMACOLOGY*

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It is my privilege to discuss certain aspects of bronchial asthma essentially produced by immunologic or allergic mechanisms. Although the origin of asthma is intimately connected with antigen-antibody reactions or allergen-antibody reactions, it will also be necessary to briefly explore the role of psychodynamics in implementing more effective therapy.[1, 2]

Let us first consider the nature of the immunologic process by analyzing the molecules responsible for pollen asthma. There is no doubt that in hypersensitive individuals, contact of sufficient pollen with the respiratory tract results in bronchial spasm as well as vasodilatation and swelling of the allergic mucous membrane. What is the nature of the molecules in the ragweed pollen granules or in timothy pollen granules which dissolve in the liquid film of the mucosa of the respiratory tract to diffuse into the tissues to cause pollen asthma?[3] One of the most characteristic properties of any molecule is its size in terms of molecular weight. Do the allergenic molecules in ragweed and in timothy grass pollens have the high molecular weights characteristic of proteins? It had been proposed that these allergenic molecules are protein in nature. If they were proteins, we would expect comparatively high molecular weights. Recall for a moment the molecular weights of some common substances. The molecular weight of sodium chloride is approximately 58; that of histamine about 111; of sucrose close to 342.

If we examine the molecular weights of proteins, it is evident that

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the smallest molecular weight found for a typical protein, namely lactalbumin, is 17,000. Where do the allergenic molecules of ragweed and timothy pollens fit into this picture? In the last decade there have been devised precise methods of determining the molecular weights and other properties of protein molecules. These methods have made obsolete a good many of the early notions of the properties of protein molecules and have led to a more scientific description and elaboration of the nature of protein and allergen molecules. These methods are electrophoresis, ultracentrifugation and diffusion. For our present purposes, only electrophoretic and the ultracentrifugal data will be discussed.

The moving boundary method of Tiselius was used to separate the molecules of giant and dwarf ragweed extract.[4]

The dynamic process occurring in the U-tube is dependent upon the fact that the electrical charges of the components of the solution are different. In this way separation is achieved by means of electrical forces. e.g., electrical fractionation. Using this electrical method, it was found that in giant ragweed, dwarf ragweed, and timothy grass as well as in other pollen extracts, the main component was colorless in the concentrations isolated and practically without any motion in the electrical field. It was biologically active.

That is, this main colorless component was in each case a powerful allergen which produced hay fever and asthma as well as positive skin reactions. There was thus isolated, what are known as electrophoretically homogeneous allergens which were the main components as determined by electrophoretic fractionation. Separated from the complicated solution of pollen extracts were many pigments, which were also biologically active as far as could be ascertained with the small quantities available.

What sort of molecules were these major colorless components in pollen extracts?[5] Were they very large molecules, as large as protein molecules or were they small molecules? Did they have chemical reactions characteristic of proteins? To ascertain the size of the essentially colorless molecules the electrophoretically homogeneous solutions were studied in an ultracentrifuge. The ultracentrifuge is really a more powerful centrifuge which is able to spin down protein molecules the way fat globules are spun down in a cream separator. The speed with which the molecules are sedimented gives an idea of the radius of the

molecule. By means of diffusion data and other characteristics of the solution, a very close approximation of the molecular weight is obtained. Study of the sedimentation velocity of the unpigmented, electrophoretically homogeneous components showed that these molecules sedimented out much more slowly than serum albumin which is a typical protein.

Sedimentation occurred more slowly because the smaller molecules are acted upon by a lesser force in the ultracentrifugal field.

By correlating the ultracentrifugal data with diffusion studies, it was found that these molecules had molecular weights of about 5,000 each. The main electrophoretically homogeneous molecule in Giant Ragweed solution was named Trifidin; in Dwarf Ragweed solution, Artefolin. A molecular weight of 5,000 is rather low for the molecular weight of a typical protein. Considering the chemical reactions of solutions of these molecules, it appeared that they were not typical proteins. The colorless component of Timothy grass was also studied in the ultracentrifuge but its molecule was so small that it was not sedimented under the conditions of the experiments.

Chemical analysis of the small quantities of these molecules available to the present time, compared with serum diluted 1:30 indicated that these pollen molecules resembled, as far as their chemical properties and molecular weights were concerned, high molecular weight polypeptides rather than proteins. To speak of these allergenic molecules as proteins is more or less fallacious, although they are to a certain extent, protein-like in nature. The name Protoproteins has been suggested for these major colorless components of pollen extracts.[1,6] The prefix "proto" denotes the first or the lowest in a series. A Protoprotein then, would be a substance on the border line between high molecular weight polypeptides and low molecular weight protein molecules. The designation of these highly allergenic molecules by the term Protoprotein not merely gives them a new name but lends to this new group of molecules an element of predictability. This predictability enables us to state that such small molecules can diffuse more readily and permeate living mucous membranes with greater facility. Also there is greater hope for synthesis in the laboratory. It is of interest to speculate that if the molecular weight of these molecules had been much greater, say one million, the probability of sensitization of the mucous membrane of the respiratory tract would be very much

less indeed, and the facility with which they could be driven into the skin by electrophoresis would be reduced to a considerable extent.

The small molecular weight may account for the rapid onset of anaphylactoid shock following a small overdose of pollen extract.

The administration of pollen extract is, in general not attended with any acute danger or repeated injury to the patient. However, certain recommended procedures increase the dose to just below the level of shock. Indeed, reports of experimentally induced mild anaphylactic shock in patients undergoing therapy is reported with little thought of damage to the patient. Recent experiments by Castberg and Schwartz may indicate a certain degree of laxity in the recommendations often advised for allergic therapy. Castberg and Schwartz[7] show that in five young hay fever patients following a shocking dose of pollen extracts important changes occurred in the electrocardiograph. In all cases, changes typical for anoxemia of the myocardium were found. Although there was no evidence to suggest any specific allergic reaction in the heart and although the authors believe that the observed changes depend upon decreased ventilation of the lungs, our attitudes in this case should be specifically connected with the welfare of the patient undergoing hay fever therapy. Just what for example, is the effect of overdosage over prolonged periods, for many years? Do doses producing subclinical shock in the tissues lead to chronic changes due to therapy? In view of the fact that this question cannot be answered, it appears desirable at present, to cautiously avoid shocking doses of allergens or doses of allergens beneath the shocking level in the therapy of hay fever and asthma. The local reaction of the patient's skin as well as general reactions are the guide to therapy rather than any particular number of units advocated for a given patient in a routine fashion. The psychological implications in the administration of sub-anaphylactic doses include a threat to the patient by the physician of anaphylatic shock and its consequences. This is unwarranted by any increased value in therapeutic result claimed or attained.

During the past six months by applying a new principle of electrophoretic separation, larger quantities of purified Trifidin, sufficient for clinical trial and chemical analysis are being prepared.[8] The study of electrophoretically purified material will lead to a better understanding of the relationship between these small allergenic molecules and sensitization.

Antihistaminic Drugs

With few exceptions antihistaminic drugs like Benadryl and Pyribenzamine have aside from their effects on the pharmacologic action of histamine, one very definite characteristic in common: their hypnotic effect. Indeed, the depressant action of these drugs is often so great that patients taking them are cautioned not to use machinery or to drive cars. This is apparently not true to the same extent for barbiturates. Antihistaminic drugs often replace the barbiturates and are frequently given combined with ephedrine. In addition to the depressant effect of the antihistaminic drugs there is also a very definite atropine-like effect which accounts for the drying of the mucous membranes in the therapy of hay fever. When antihistaminic drugs are prescribed in allergic disorders, are we prescribing these drugs to counteract the effect of histamine or are we prescribing them for the hypnotic and atropine-like action combined with a decrease in the permeability of the small blood vessels?[9]

The newer antihistaminic drugs may operate by competing with histamine or similar molecules for the positions within the cells of the tissue. Whether this competitive mechanism is correct or not, the drugs certainly prevent the action of histamine itself under certain circumstances. This antihistaminic action is especially marked with high concentrations of the drug. They should be used with caution in asthma and are often contraindicated because of the atropine-like action. When they are effective in asthma it should be borne in mind that they may be so because of a hypnotic action rather than an antihistaminic effect. In the presence of anxiety, the hypnotic effect of the antihistaminic group is often observed. In spite of value as a hypnotic, the atropine effect is often a reason for contraindication. The atropine effect leads to drying of the mucous membranes, thickening of the secretions, prevention of the clearing of the respiratory tract of mucopurulent materials and therefore interferes with respiration. This is particularly true if the patient has been given other sedatives. The combined pharmacological action of these very powerful depressants with ordinary sedatives is unpredictable on the basis of available data. Another probable contraindication, at present, to the use of antihistaminic drugs, is the presence of infection. There has been a tendency to prescribe these powerful agents independent of the nature of the

illness. Dr. B. S. Halpern of Paris was recently asked at the end of a lecture whether or not, in view of the effect on the capillary permeability of the antihistaminic drugs, there was any influence on the immunologic reactions of the patient. Dr. Halpern pointed out, that although experiments were in progress, the effects on antibody formation were relatively unknown.

It is necessary to recall that there are other drugs which are more truly antihistaminic in their pharmacologic action. Notably amongst these is epinephrine. The antihistaminic effect of epinephrine and other sympathomimetic amines in many times (thousands of times in the case of epinephrine) greater than that of drugs similar to Benadryl and Pyribenzamine. In addition to having an antihistaminic effect, epinephrine also shows the restoration effect.[10] That is, many hours after epinephrine neutralizes histamine in the skin by vasoconstriction (a true pharmacologic antagonism) the epinephrine again may manifest itself by vasoconstriction at the site of histamine action. Similar general reactions were observed first by Cameron[11] who found that histamine neutralizes the general effect of epinephrine only in a transient fashion. These observations make unlikely the theory that epinephrine liberates histamine in a quantity of pharmacologic significance.

Aerosols

General: The use of aerosol therapy in asthma is not new. Steam inhalations and inhalation of the smoke from burning stramonium leaves are early but still useful examples of aerosol therapy of the bronchi. Many pharmacologically active drugs have been employed. Here the discussion will be limited to ephinephrine and penicillin aerosols produced by oxygen or air pressure. The weight and therefore, the dose of the particle of the drug is proportional to the cube of the radius of the particle. In aerosol therapy of the lungs, therefore, if topical therapy is the therapeutic goal, the results essentially depend upon the dose of the drug delivered to the patient at the site where the dose is to be applied topically.

According to Findeisen,[12] particles of 3 micra and above are taken out completely by the trachea, bronchi, bronchioles and the aveolar ducts. Particles of 1 micron radius and above are removed by the lungs to the extent of 97 per cent with 3 per cent recovered on expiration.

As the radius of a particle gets smaller, particles of 0.3 micron radius are absorbed to the extent of only 35 per cent with 65 per cent recovery on expiration. These conclusions of Findeisen are confirmed by the experimental work of van Wijk and Patterson[13] who showed that solid particulate material of 0.6 micron radius was removed to the extent of 63 per cent while particles ranging from 0.6 micron radius to 2.0 micra radius were removed from 63 per cent to 96 per cent. Particles less than 0.4 micron in radius were retained to the extent of about 30 per cent. All of these data support the point of view that rebreathing equipment is unnecessary in routine aerosol therapy. With a suitable nebulizer and the proper technique of having the aerosol inspired with the initial phase of inspiration, excellent therapeutic results have been obtained by direct inspiration of the aerosol from the nebulizer without a rebreathing bag or other complicating equipment.[14, 15]

Epinephrine: One of the most useful methods of treating asthma is by the nebulization of a 1:100 epinephrine salt solution provided that certain conditions are fulfilled:[16]

1. The droplets are stable and do not evaporate rapidly.
2. Therapeutically suitable particle size distribution is achieved.
3. Nebulizer delivery is adequate.

There are many different types of nebulizers available commercially. These are reviewed in an interesting and excellent article by Harsh.[17] Added to the nebulizers enumerated by Harsh should also be mentioned as meritorious a double jet nebulizer made available recently.

This double jet nebulizer has many interesting features and is worthy of further investigation in aerosol therapy. In general, ordinarily commercially available solutions of epinephrine, evaporate too rapidly on leaving the nebulizer. A vertical nebulizer is preferred since a horizontal nebulizer increases the danger of swallowing the solution. Certain nebulizers, horizontal in construction, however, deliver excellent mists and are suitable if the patient is careful. Once the nebulizer has been chosen it is important that the nebulizer operates efficiently with the solution employed. In spite of the fact that 1:100 epinephrine solutions appear with various names as pointed out by Harsh, the important feature of all of the solutions is the fact that they contain about 1 per cent biologically active epinephrine. Other sympathomimetic amines related to epinephrine are also available for nebulization but

whether they are as suitable as epinephrine for nebulization therapy in asthma is still a matter for further clinical study.

It is important to instruct the patient that the nebulizer performs satisfactorily only when delivering a fairly stable, visible, dry, mist. The stability of the mist is critical because if the particle size is not correct, evaporation of the particles occurs and effective deposition of the epinephrine droplets in the lungs may not occur. In order to stabilize the epinephrine solution, at least 10 per cent of glycerine is desirable. U. S. Army Stock Item No. 1,175,320, July 16, 1945, employs 25 per cent of glycerine. I believe that this concentration of glycerine is a suitable stabilizing agent and is better than the 50 per cent of glycerine which I recommended in 1940.[16] The presence of 25 per cent of glycerine prevents rapid evaporation of the particles and thus gives a particle size suitable for therapy. This concentration of glycerine brings aerosol therapy with epinephrine into an area of optimal predictability. The difficulties encountered often arise because of the lack of predictability in both nebulizer and solution, each of which contains variables which are not controlled. The favorable clinical experiences with approximately 25 per cent of glycerine are borne out by the experimental work of Bryson, Demerec, Laskin and Potter (Seventh Monthly Progress Report to Contract No. 266, CWS 246 between the War Department and the Long Island Biological Association Inc., October 10, 1943), who showed glycerine aerosols of the greatest persistency are achieved with solutions containing 30 per cent of glycerine. A plateau is maintained with glycerine concentrations up to 70 per cent but optimal values were obtained at 30 per cent. This confirms clinical observation that about 25 per cent of glycerine gives the optimal predictability for aerosol therapy with epinephrine solutions. Most cases of mild to moderate asthma uncomplicated by other factors (e.g. anxiety neurosis) are readily controlled by aerosol therapy with stabilized epinephrine solutions.

Epinephrine salt solutions should preferably be between pH 4 and 5. This is readily obtained by titrating 1 gram of epinephrine base with approximately 5.2 cc. of molar phosphoric acid and diluting to 100 cc.

Failures with this type of therapy may usually be traced back to:

1. Insufficient solution being used in the nebulizer.
2. A poorly constructed nebulizer.
3. Insufficient glycerine or other stabilizing substance.

4. An excessive amount of secretion in the bronchial tubes preventing access of the aerosol to the points required.

5. An emotional state of the patient, e.g., anxiety[18] in which sympathomimetic amines are essentially contraindicated except in very small doses. Very often patients in an anxiety state are called "epinephrine fast." The epinephrine "fastness" of these patients is not always due to the fact that epinephrine has been employed. Indeed, "epinephrine fastness" can be observed in several categories:

a. When epinephrine has not been used for some time.

b. When only a small amount of epinephrine has been administered.

c. When a considerable amount has been administered.

In view of the fact that "epinephrine fastness" can occur when there has been no opportunity for a true pharmacologic tolerance to be achieved as under a, and b, it is important that the emotional state of the patient be considered. Epinephrine should never be administered if it is not obviously effective. If ephedrine derivatives by mouth are not satisfactory, the patient should be instructed to use epinephrine aerosol wherever possible to prevent an impending attack. In this way, the excellent results obtained with epinephrine aerosol therapy justify the statement that in most instances inhalation can replace injection.

Still commonly used are aerosols formed by burning stramonium leaves. These aerosols may be obtained by either burning the powder on a small dish or by smoking stramonium cigarettes. The clinical effectiveness of these smokes is presumably due to the presence of stramonium. However, the active biological agents in these aerosols have not been chemically isolated and identified.

Clinical data are available on other aerosols: aminophylline, theophylline, atropine as well as substances similar to epinephrine itself.

Penicillin:[14, 15, 19] Penicillin aerosol is indicated in the therapy of asthma if it is believed that penicillin susceptible organisms may be present and if the presence of these organisms is producing an infection which requires antibiotic therapy. This is true independent of the origin of the asthma. The asthma may be produced by allergenic molecules such as pollen with secondary infection, by bronchiectatic processes or by other types of lesions leading to secondary infection of the lungs. The administration of penicillin in cases of this type should not be restricted to its use in aerosols. Simultaneously, injection of the antibiotic should be carried out. In addition, penicillin aerosol therapy

should be preceded by an aerosol of epinephrine 1:100 to reduce narrowing of the bronchial tubes. As far as the concentration of the penicillin is concerned in the aerosol, the main error is administering too small a dose and concentration. Aerosols are preferred with concentrations of penicillin of at least 200,000 units per cc. with the oxygen flow about 6 liters per minute by mouth or at 10 liters per minute if nasal tips are employed. It should be ascertained if the nebulizer employed functions efficiently at 10 liters flow per minute. The minimum of 50,000 units per cc. with oxygen at 6 liters per minute 2 or 3 times daily is permissible. Preferred, is at least 500,000 units administered in 2 cc. at least twice daily with nasal tips, if possible. Certain commercially available nebulizers are adapted for these procedures. The details[14, 15, 17] may be found elsewhere but the output at 10 liters per minute should be confirmed by checking the delivery of the nebulizer by standard dyes.[20]

The recent commercial introduction of penicillin dust brings up an important point. The mean particle size of one of these dusts[21] is so large that only a small fraction of the dose is in small particles. If the therapeutic claims are justified, and this requires further evidence, how can we explain the therapeutic results, assuming them to be correct? Is the theory concerning particle size distribution incorrect or do we have an unexpected and new technique? If we examine the fate of Lipiodol, which can be atomized into the lungs employing a DeVilbiss atomizer (No. 152) a bronchogram is obtained following the deposition of the Lipiodol in the trachea and bronchi.

The same thing might occur, although this has not been definitely proven, when large particles of the penicillin dust are breathed in through the mouth. A certain fraction of the large particles may pass the larynx and adhere to the trachea and bronchi. The penicillin may then through gravitational forces pass to one side or the other of the respiratory tract, depending upon the position of the patient in the same way as that depicted for Lipiodol. It does not appear likely that penicillin dust of this type can supplant aerosol therapy with the nebulizer. The particle size distribution is very different, indeed. Judging by what has been covered in regard to the particle size distribution in the lungs it is inconceivable that the same distribution can be achieved with large particles that can be obtained with small particles. In the case of small particles, the particles are fairly uniformly distributed throughout

the bronchial tree by the force of the convection current of inspired air. In general, according to theory and experiments, deposition of large particles must occur in the upper part of the bronchial tree with partial drainage to the lower part of the bronchial tree dependent upon accidental factors, especially gravity.[22]

It is pertinent to the mechanics of the therapeutic effects of aerosols comprised of either liquid or solid particles to know that as the particles are floated in the air through the bronchial tree some material will be deposited whenever a corner is turned by the aerosol. For example, as the aerosol turns a corner about a purulent deposit, some of the aerosol is deposited on that part of plug facing the aerosol flow. This can be shown experimentally with dyes.

If a minute mass of gelatin or agar is placed in a glass tube and an aerosol of a red dye is passed through the tube, deposition of the dye on the side facing the flow of the aerosol is readily observed. This apparently insures automatic deposition on purulent material in the line of flow. This phenomenon can also be seen following the administration of phenolsulfonphthalein aerosols to patients with lung infections. The mucopurulent material coughed up is often mainly colored on one side with the dye diffusing toward the other part of the material. In all likelihood, penicillin aerosol deposits in the same way in the respiratory tract wherever corners are turned for mechanical reasons of any kind.[15]

Narcotics

In spite of the fact that asthma is a chronic disease with a comparatively long life expectancy, narcotic drugs known to be habit forming and coming within the scope of our narcotic laws are still being widely used. An extreme example of this, was a recommendation to the daughter of a patient whom I saw in consultation, that the daughter, as a nurse, could administer morphine intravenously to her 75 year old mother in status asthmaticus. What the pharmacologic reason was behind this suggestion is puzzling since morphine often causes death in patients of this age. There does not seem to be much diversity of opinion that morphine is contraindicated in asthma not only because of its depressant effect but also because of the probability of habituation. Related drugs like meperidine hydrochloride (Demerol) also come under the narcotic laws. These drugs are also respiratory depressants.

Therefore, Demerol and similar substances are contraindicated in older patients because of their depressant action and should not be prescribed for younger individuals because of the danger of habituation. The serious consequences of addiction cannot be disregarded. The anxious patient who requires quieting can be treated by ways other than those provided by habit forming narcotics. If the therapy of asthma depends upon habit forming narcotics then psychotherapy is indicated.

Psychodynamic Pharmacology and the Therapy of Asthma

Although the respiratory difficulties under discussion have a basic etiologic structure, immunologic in nature, the intensity and persistence of asthma is maintained in many patients because of the presence of unconscious conflicts which lead to difficulties in the conscious, realistic realm.[23] The nature of these conflicts in allergic individuals has been in part determined by psychoanalysis. It is well for us to clarify the relationship by what is learned by psychoanalytic procedures to the practical therapy of the asthmatic patient. While it is desirable, and indeed essential for the physician to understand the relationship of unconscious conflicts to the origin of asthma, the material obtained by psychoanalysis should not be the subject of direct discussion by the physician and patient. I mention this because publicity in the daily press has recently been given to unconscious material derived from psychoanalytic studies of asthmatic individuals. It is questionable if the asthmatic person should be suddenly confronted with unconscious material of this type in press reports. Certainly the well trained analyst would consider this in actual practice as one of the gravest of technical errors.

To illustrate what is meant by the unconscious, may I utilize an analogy. There are here in New York City, two methods of projecting motion pictures. The type most commonly used is that in which the light is passed over the heads of the audience onto a reflecting screen. Portrayed on the screen is a realistic pattern of activity readily observed by the audience. The origin of this pattern is easily traced back to the projector which throws these realistic images on the screen. These images on the screen correspond to the clinical manifestations of the patient which are accessible and observable. The second type of motion picture projection is commonly found in newsreel theatres. In this type the same activity is readily visible on the screen but there is no orienting beam of light to be traced back to the projector. The screen in this case

is both reflecting and transparent. But the projector is invisible and is situated behind the screen. There is no way of immediately deriving from the realistic activities on the screen, the hidden mechanisms embodied behind the screen in the projector. The unconscious mechanisms of the patient are just as hidden from the physician, perhaps more so, than the projector in the newsreel theatres where the projector and the sound track are behind a screen and not available to the observer of the screen except by passing to the area behind the screen. The procedure of psychoanalysis elicits unconscious material by determining in part the psychodynamic mechanisms which result in realistic activities observable to the physician. Although it is necessary to recognize that mechanisms behind the screen of conscious activities of the patient determine his symptoms and complaints, it is usually difficult to utilize them directly in the treatment of the acutely ill asthmatic patient. We should be more concerned with recognizing the general psychologic pattern by means of which he deals with his inner stresses, in conjunction with utilizing the action of drugs in an explicit relationship to the immediate, dominant emotional state of the patient. It is necessary, therefore, to recognize and to utilize the *psychodynamic pharmacology* of drugs like epinephrine, the barbiturates, etc, used in the treatment of asthma.

It was first shown by Eduardo Weiss[24] and by French and Alexander[25] and their group as well as by others, that the outstanding psychodynamic process in the asthmatic patient is the unconscious fear of the loss of the mother or mother image or parent figure. These unconscious psychomotive forces, developed early in the life history of the patient, are modified and diverted by the psychological, physical and cultural growth of the patient, with this fundamental and unconscious pattern of anxiety however, persisting. The intrusion of other psychomotive forces may change the syndrome observed in asthma so that the patient almost always presents a mixed syndrome with certain features outstanding. In the following brief and schematic classification of asthmatic patients, the dominant affective tone which the patient exhibits is taken as the guide to therapy and pharmacologic measures should be initially adapted to the impression made after studying the patient as a whole. Often the drug administered will intensify the neurotic pattern and thus confirm the diagnosis by increasing the severity of the symptoms. With this concept in mind

some additional aspects of psychodynamic pharmacology of the therapy of asthma will be outlined.

The Anxious Asthmatic Patient.[26] An undercurrent of anxiety characteristic of chronic disease is especially prominent in all cases of bronchial asthma. Interference with breathing is always a threat to life. This is well emphasized by the frequent occurrence of psychoneuroses following minor gas injuries especially noted in World War I and in industrial accidents at the present time. Another instance which illustrates the special attitude toward lung injuries was that of volunteers in the last war toward experimental production of mustard burns. Volunteers were readily obtained for experimental skin lesions but great reluctance was encountered when inhalation experiments were suggested even though reassurance was given that no permanent injury would result.[27] This undercurrent of anxiety may become a dangerous undertow in the asthmatic patient. The danger lies not only in the immunologic and psychologic realms but also in overtreatment by the physician. Indeed, it is well recognized amongst allergists that many cases of bronchial asthma are subjected to pharmacologic traumata, where the drug intensifies the symptoms because of the mental state of the patient. If we accept the point of view that an undercurrent of anxiety exists, practically speaking, in all cases of asthma, it is important to search for symptoms connected with anxiety. For example, in taking the history it is necessary to ascertain if the asthmatic attacks started by difficulty on inspiration or difficulty on expiration. The respiratory cycle, in many cases, must be carefully explained to the patient. However, after the patient understands the respiratory cycle, instead of saying that the attack was asthma, the statement may be made that there was difficulty getting air in or in catching the breath. Difficulty in catching the breath or in getting the breath is not equivalent to a classical attack of asthma. In classical asthma of course, the difficulty is on expiration. If there is difficulty on inspiration, and especially if the attack of asthma begins with difficulty on inspiration, it is wise to administer, in very small doses, epinephrine, whether by injection or inhalation, or, ephedrine and related substances orally. This is necessary because epinephrine itself is apt to produce anxiety in larger doses.[11,18] Very often difficulty on inspiration develops into a mixed syndrome with difficulty on expiration dominating the picture. The underlying anxiety is just as important a part of the pattern that has to be treated as the difficulty

on expiration which under ordinary circumstances responds to the sympathomimetic amines.

Another aid in determining the degree of anxiety is by observation of the patient's oxygenation. If the action of the chest muscles is great and the color is good nevertheless, it may be desirable to use oxygen with the understanding that the response to oxygen in a case of this type may be more of a test for an underlying neurosis than an active therapeutic procedure embodying pharmacologic action. Patients of this type often respond almost immediately to oxygen. Indeed, it is frequent to have a patient claim relief within one minute after having the tube with oxygen passing through it, placed in the mouth. Sometimes, relaxation follows merely placing the tube in the mouth even before the oxygen starts to flow. Anxious patients may often refuse to go into the oxygen tent or wear an oxygen mask. This anxiety is important because it reflects a phobic component in the patient's make-up. The use of sedation in patients with anxiety is usually indicated. Chloral hydrate with or without the barbiturates is very effective. There is no routine dosage. The dosage depends upon the pharmacologic response of the patient as well as his character structure. This is of importance in certain cases where sedation leads to regression to an infantile level, thus decreasing the coöperation and increasing the infantile behavior.[28] The predominantly anxious type will often speak of dying during the attack. Reassurance is desirable, even if the patient himself does not suggest the possibility of death. It is always wise to make certain that the patient understands that asthma is a chronic disease that can be prevented from becoming serious if he coöperates with the physician.

The Depressed Asthmatic Patient. In certain cases the asthmatic patient is found to be an ostensibly submissive and obedient patient. His submissiveness and obedience very often are a reflection of a depressed attitude. In these patients it is very wise to study the effects of sedation which may under certain circumstances, be contraindicated because of the effect on the depression itself. The depressed patient will very often prefer to have epinephrine by injection rather than by the nebulizer because of the stimulating effect of the injected epinephrine. Very often the depressed patient will say that he feels better after an injection of epinephrine even though the severity of asthma has hardly changed. The depression should be treated cautiously as with other depressed states by the administration of small doses of amphetamine sulphate,

after breakfast and after lunch. It is desirable that the patient be told of the possible effects of the amphetamine sulphate and that doctor and patient should work together to determine the optimal dose. Even though amphetamine is taken by mouth, epinephrine, as an aerosol is not contraindicated nor are small doses of sedatives in the evenings and at bedtime. An extreme example of a depressed patient is the type who meets a new physician with a statement similar to, "No one can help me. I have seen many physicians and I am still ill." It is important to recognize that these patients are ill psychologically and that they do not respond to ordinary therapy. Indeed the patient who says, "No one can help me," very frequently is correct. Increased danger of death from causes other than the asthma, such as coronary closure is present. Just what the best procedure is in this type of patient is uncertain from the allergist's point of view. Ordinary routine measures recommended for the therapy may often fail. Intensive psychotherapy, if acceptable to the patient, may be indicated. Chemical hypnosis for the patient who states the equivalent of, "No one can help me," might be a desirable procedure in order to elicit rapidly the basis of the patient's desire to retain a negativistic attitude toward therapy.

The Grieving Asthmatic Patient. The grieving type of patient is, as the name implies, an unhappy person who is, in all likelihood, substituting for what may be an unrecognized feeling of grief, the asthmatic spasm. The grieving asthmatic patient represents a syndrome often mixed with dependence and depression. This may be observed in patients immunologically sensitive to pollens who have pollen asthma prolonged without suitable reason into the winter months. The patient may be a dependent person with a strong conscious and unconscious dependence on the mother or parent figure. It is important to recognize this syndrome and make certain that the physiological needs of the patient are taken care of with suitable reassurance and minimal use of sedation and of the sympathomimetic amines. Breathing exercises accompanied by an expiratory hum or moan may be prescribed hourly. The expiratory hum aids the patient apparently to express as a cry the unconscious anxiety mentioned. Indeed in a patient whom I have observed over a period of years the expiratory hum almost inevitably prevented asthmatic spasms. The patient by merely thinking of the expiratory hum in the subway, for example, would prevent the attack.

The Hostile Asthmatic Patient. The hostile patient very frequently

camouflages his attitudes by apparently coöperating fully with the physician. The sympathomimetic amines, either by injection or by aerosols should be used with caution. In this type sedation is effective and regression to an infantile level because of the sedatives is not as frequent. Patients of this type can often take 3 grains of sodium amytal, four or five times daily and still function fairly well under hospital conditions. Their severe asthma for which hospitalization was instituted may disappear in a matter of days. Frequently, upon moving a patient of this type to the hospital, the factors inducing the hostilities are diminished so rapidly that mild sedation is all that is needed to break the severity of the asthma. In children, removal from a threatening environment may result in cessation of the asthma provided that a substitute mother figure is provided.

The Dependent Asthmatic Patient. Certain patients showing anxiety, especially children, may make neurotic utilization of their asthma in order to obtain attention from a parent or a parent figure. In the young child, as we know, the conscious and the unconscious are not as clearly defined as in the adult. Utilization of asthma is often frankly admitted by the child. Frequent examples of this are cited in the literature. In the adult the dependence upon the parent or upon the husband or wife playing the role of the parent figure should be observed, noted and utilized in therapy. The therapy of these patients should include in the home a routine in which constant reassurance and support are given. Excessive doses of epinephrine which increases anxiety should be avoided. Moderate sedation and small doses of the sympathomimetic amines, whether by aerosol, by rectum or by hypodermic is indicated. Realistic attention to the symptoms with emphasis on the detail of the symptom often reassures the dependent individual that his wants are being cared for and decreases the asthma.

The Phobic Asthmatic Patient. Although not so common a type, the patient complaining of bronchial asthma whose main symptom is difficulty in breathing with a feeling of constriction of the chest accompanied by a minimal quantity of wheezing often is a phobic type of person who is afraid of the street and who has many fears such as claustrophobia, fear of elevators and other common fears which restrict his activities. Examination of the chest often reveals that the vital capacity is diminished even though breath sounds are good and there is no emphysema. In one patient, whom I had occasion to study over a

period of years, the vital capacity was unchanged by the administration of epinephrine aerosol but there was definite relief of the feeling of restricted motion in breathing. The epinephrine aerosol produced no change in the chest signs. Apparently the reassurance given by the nebulizer in the mouth plus a small dose of a sympathomimetic amine resulted in improvement in the feeling of the constriction of the chest. This patient, who has refused psychotherapy, has used epinephrine aerosol for many years to relieve what she considers to be asthma but which really is a feeling of constriction in the chest which most often occurs without any signs or symptoms of asthma but with feelings of anxiety. In order to avoid any misunderstanding in regard to the psychotherapy of the asthmatic patient, it should be noted that I believe that for the best results psychotherapy should be in charge of an allergist with suitable psychiatric training or of a psychiatrist with an understanding of the immunological aspects of asthma. It is not intended that the writer anywhere implies that unconscious material should be casually employed, or that the general practitioner should utilize techniques of deep psychotherapy.

May I now summarize how the use of powerful sympathomimetic amines, antihistaminic drugs, sedatives and antibiotics in the treatment of bronchial asthma should be oriented. While it is generally agreed that therapy should not neglect the physiology and the immunology of the patient in the asthmatic state, the personality of the patient cannot be omitted in planning suitable therapeutic procedures. It is neither wise nor desirable for the patient suffering from severe asthma to be reminded of unconscious material that the doctor himself may be aware of. It is more than desirable in our present state of knowledge to use pharmacologically active drugs in connection with the total personality of the patient manifested during the acute asthmatic attack. Whether anxiety, phobia, depression, dependence, hostility, grief, or other pattern dominates the asthmatic attack, the physician should bring into the proper sphere the psychodynamic pharmacology of the drug employed in treating both the asthmatic spasm and the personality of the patient himself. In this way a better understanding of the action of the drugs on the personality of the patient will be obtained with much greater predictability in the therapy of bronchial asthma.

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MEDICINE UNDER MUSSOLINI*

MARIO VOLTERRA

IN THESE uneasy times in which we are living it is proper and—let us hope—useful to look back at the past for guidance and inspiration. We agree with the organizers of these meetings of the Historical Section of The New York Academy of Medicine, that history includes not only ancient times, the Renaissance, or the triumphal era of scientific and medical progress of the 18th and 19th centuries, but also the years just past. With this idea in mind I was asked to trace the influence of a dictatorial, totalitarian regime on medicine and medical education in Italy. I wish to express my gratitude for having been given this opportunity.

It is my intention to present an objective report giving proper stress to both the bad and the good developments in Italian medicine from 1922 to 1943, the period of the fascist regime. I will tell you right now that the balance will not turn in favor of that regime, which unfortunately did not fail now and then to get some praise even from some democratic countries.

In order to have the proper perspective it is necessary to recapitulate very briefly what Italian medicine represented and contributed during the last century and what its situation had become in the 1920's. I shall recall to you a few of the names connected with important medical developments, trusting that the majority of them will be familiar to you.

The brilliant tradition in anatomical studies which reached its highest point with Morgagni (1682-1771) was maintained during the 19th century by Scarpa, Corti, Pacini, and at the end of the century by Golgi. Golgi's contribution was twofold. His researches in neuroanatomy were recognized by the award of the 1906 Nobel Prize conjointly to him and to Ramon y Cajal. His research on malaria is also of high importance. In the field of pathology and pathological anatomy

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there were two world-famous men: Banti, who is remembered for his work on the spleen and on hemolysis, and Marchiafava, who contributed fundamental studies on malaria and later described paroxysmal nocturnal hemoglobinuria with hemosiderinuria, also known as the Marchiafava-Micheli Disease. In the spring of 1901, when Harvey Cushing was working on the relations between intracranial pressure and blood pressure he went to the laboratory of Angelo Mosso, the Turin physiologist, to complete his research. Among well known medical men let me mention Forlanini, whose fame is connected, as you know, with the discovery and clinical application of therapeutic pneumothorax in tuberculosis, and among the surgeons Bassini, who developed the first rational operation for hernia. To this list of medical men I like to add Cesare Lombroso, the criminologist, and the zoologist Grassi, who discovered the role of mosquitoes in the transmission of malaria.* I beg you to consider that these few men were able to achieve universal fame through the sheer value of their work. They spoke and published in a language which is comparatively unknown outside the boundaries of their own country, a country which has little political weight and which is thought of generally, though unjustly, as being rich only in natural beauties and artistic tendencies but poor in scientific achievements. And these men were, all of them, modest and even shy. They were men who did not come out of their universities to cultivate international contacts.

These men are mentioned here because their fame spread beyond the confines of their country, but others should be added who worked in every field of medical research and whose names are found when one looks diligently through the literature. Some of these were famous teachers who had a powerful influence in molding the minds of several generations of good doctors, at a time when the personality of a teacher not rarely had the power of leaving a permanent imprint on the intellect and character of the student.

The doctors who were educated in the medical schools of Italy in the late 19th century were for the greater part good general practitioners, well schooled in the art of questioning patients and examining them with the most minute resources of a painstaking physical examination. They were, of course, poorly provided with effective means of treatment. They were modest and honest, and—I gather—not dissimilar

* The Nobel Prize for this discovery went to Ross, who demonstrated the infection of birds by means of the mosquito but it was Grassi who proved experimentally that malaria is transmitted to man by infected mosquitoes.

to the doctors of France or Austria, of Great Britain or the United States.

In the first two decades of the 20th century the picture started to change. Although some of the men to whom I have referred were still active as research workers or teachers and although their schools still produced new generations of young scientists and clinicians, it seemed as if a strange debilitating process had set in which was progressively reducing the productivity of these institutes and clinics, as far as quality is concerned. Looking at this process now, retrospectively, it seems to me that the explanation of this unhappy event may be found, at least in part, in the progressively extending gap between the material set-up of Italian medical institutes and the increasing technical complexity of medical research and teaching. Until the end of the First World War the great majority of the medical university institutes in Italy were located in old quarters, badly cut up from ancient and antiquated hospitals or monasteries. These establishments were usually deficient in technical facilities such as hot water, steam, and vacuum. Very often they even lacked a sufficient heating system. What is still more important, they operated with a ridiculously low annual budget which included reagents, animals, gas, electricity and even salaries of technical personnel. To sum up, the equipment of the institutes and clinics had not changed essentially from that which had prevailed in the previous century, at the time when medicine was only emerging from the field of simple—and inexpensive—speculation.

With the increasing complexity of biological and medical problems another insufficiency of this system became more and more acute. In order to achieve some success in modern medical investigation a certain amount of team work is almost always necessary. Even for efficient teaching the help of a large staff of well-prepared assistants is indispensable. The choice and training of good assistants is, of course, primarily the responsibility of the chief of the institute, but his task cannot be carried out if the conditions under which the assistants are supposed to work are such as to make their life financially insecure and spiritually unsatisfactory. During the period when medical research was essentially morphological and clinical teaching was predominantly theoretic—as was the case until the first decades of this century—the lack of laboratory facilities and the insufficiency of the staff was not felt. These factors did not prevent the Italian medical schools from

participating actively and with honor in the scientific arena and did not prevent them from preparing good medical men capable of practicing medicine according to the standards of the time. But when medical research became increasingly based upon physiological, chemical, and immunological foundations, with the accompanying expensive technical paraphernalia, the newer generations of investigators were hampered more and more in their work. Medical teaching became stale and medical practice antiquated. It is really remarkable, and a proof of the perserverance and spirit of these workers, that several Italian medical schools were able to maintain medical research at all and were even able to produce some prominent men, such as Micheli, the clinician of Turin; Ferrata, the hematologist of Pavia; Putti, the orthopedic surgeon of Bologna; Cerletti, the neurologist of Rome, the originator of electro-shock; G. Levi, the histologist of Turin.

This was the situation prevailing at the end of the First World War. Among the many problems of reconstruction and modernization which faced Italy, some of the most urgent were the reform of higher education, the modernization of health administration, and the rejuvenation of medical practice.

In Italy fascism was born and was triumphant in the fall of 1922. The effect of its policy upon medicine was gradual and started to make itself apparent only around 1925. Let us recall a few of the most important developments.

In the general reorganization of the universities, which was a part of the reform executed by the Minister of Education, Giovanni Gentile, the medical schools, which were eighteen in number, were increased to twenty through the creation of the medical faculties of the two new universities of Bari and Milan. Meanwhile, new plans were made and the old ones pushed forward for the construction of new institutes and clinics. These were gradually completed during the space of some ten years. In this way new buildings were erected in Milan, Parma, Florence, Siena, Rome, Perugia, Cagliari, and Sassari. It is to be regretted, however, that while these new buildings were provided with completely modern facades and designed with that architectural good taste which makes pleasant the look of so many Italian public buildings, the internal arrangement of these institutes very often did not include many of the modern facilities and appliances which are necessary today for research and even for routine

work. The interest of the planners and the money of the State were dedicated to outward appearance rather than to the provision of implements for working. There is no doubt in my mind that the reasons for these incongruities were several: first and foremost, that love for appearance, which not rarely amounted only to bluff, that was characteristic of the fascist regime in every field; second, the fundamental lack of understanding of the needs of serious research, and even of its usefulness and importance among national activities, which was also typical of the fascist mentality; and third, the vanity of the planners, both architects and chiefs of the institutes, who were willing to sacrifice good work for good looks. This regrettable tendency was encouraged by the very simple method of allotting relatively large sums for the construction of new buildings and little or none for equipment. Moreover, the old annual budget destined for the maintenance and operation of the institutes was not increased or at least not greatly enough to permit a change from the inefficiency which had prevailed in previous decades.

In spite of all of the claims of the government that the fostering of the national culture and the increase of its international prestige was among its first aims, nothing was done to improve the spiritual and material condition of the university personnel. The National Association of University Assistants, a progressive body which had emerged after the First World War as the spokesman of the university staffs, was very soon taken over by the fascists, purged of all its liberal elements, and transformed into an organization of political vigilance. In this way the university assistants found themselves enclosed in a net of espionage which threatened their present and their future. Do not forget that in Italy the universities belong to the State and the future of the career of any assistant or professor is in the hands of the State. It was only because fascism had great difficulty in destroying the spirit of independence of the old class of professors, that for several years political pressure did not influence their judgments in the nomination of the new professors. But after 1932 the resistance of the ranks of old professors had started to dissolve and conformity, or at any rate passive obedience, was required from everyone in a university career. In 1931 an oath of allegiance to the regime was decreed and requested from very university employee, professors included. In 1932 proof of membership in the fascist party was made obligatory for those who

wished to become full professors, just as the birth certificate, the criminal record, and the documentation of teaching activity were required. The alternative was disruption of the university career. For many men this involved the loss of their only source of income, not to speak of the political persecution which was to be expected as a consequence of what amounted to an act of rebellion.

Since the percentage of convinced fascists was very small and since everyone knew this, the obligation to take the fascist oath and the inscription in the fascist party against one's own convictions were great humiliations and certainly resulted in no increased morale among the members of a class which can hardly keep its prestige after the loss of self-respect.

Although a reform of instruction was one of the first important acts of the new regime, this reform affected the secondary schools mostly and failed to change the methods of teaching in medical schools. Medical teaching remained theoretical and consisted of amphitheatre lectures, even in clinical courses. Practical exercises were also in the curriculum but were usually restricted to a few hours a week and moreover were severely handicapped by the large number of students and the scarcity of facilities. Since the conduct of laboratory exercises and clinical seminars falls on the shoulders of the assistants, and these men, as I have said, were dissatisfied, the practical teaching of medicine did not improve. The way in which doctors were prepared for their profession during the fascist regime was not different from that which had prevailed before.

While this was the picture as far as undergraduate teaching was concerned, very little opportunity was offered by the medical schools for postgraduate education, and none for keeping the practicing physicians up-to-date. The only postgraduate education available was that open to a few men who had special financial resources and could remain in the university institutes for several years after graduation. Such men acted as assistant professors. In this way the title of "libero docente" was acquired, corresponding to the German "Privatdozent" and to the French "agregé." This title, however, was usually desired as a means of acquiring a better practice. The institution of free teaching, which is characteristic of continental universities and which is capable of rendering good service in medical education, was not substantially improved by the fascist reform. Well-organized refresher

courses for medical practitioners were lacking, as before; no effort was made to extend to these practitioners the opportunities offered by the educational mechanism of the universities.

While the governmental program, which consisted of the erection of new buildings and new clinics, was unable to change Italian medicine as far as scientific research and medical education were concerned—for reasons which I have attempted to indicate—it had some effect in the field of public health, where with an eye to political advantage, efforts were directed not only toward the expansion of buildings but also toward lengthening the rosters of government employees. Two gigantic problems of public health have always defied the action of every government in Italy. These are tuberculosis and malaria. Mortality from tuberculosis was 154 per 100,000 inhabitants in 1924. Malaria prevails in Italy only in a few comparatively limited coastal areas and in the two islands of Sicily and Sardinia. Although this disease presented no great problem from the point of view of mortality—there were only 4,000 deaths from malaria in 1924—it presented a considerable problem in terms of morbidity and economic losses. Thus there were 251,000 reported cases of malaria in 1924 alone.

The fight against tuberculosis was conducted along several lines. With the construction of new sanitaria and specialized hospitals the number of the beds available for tuberculosis patients, only 13,800 in 1935, was increased to 51,300 in 1940. Campaigns for the dissemination of elementary knowledge of this disease among the laity were conducted every year. Children and young people, being especially vulnerable, were sent to marine colonies and mountain camps every summer. All these measures, but particularly the last, which used to impress even foreign observers, were really effective. By 1940 the Italian mortality from tuberculosis had been reduced to 75 per 100,000, which was not much above the 1930 level of the United States (70 per 100,000).

Malaria was also attacked simultaneously from different angles, as it should be. Antilarval campaigns were intensified, the reclamation of coastal swamps was conducted on a very large scale, the organization of antimalarial stations, which still remained far from perfect, was improved. An Institute of Malariology was created in Rome, where it would do good work because it could use the collaboration of the excellent malariologists with which Rome has always been well pro-

vided since the times of Baccelli, Grassi, Celli, Marchiafava, and Bastianelli. In this work the Rockefeller Foundation was of great help. Mortality from malaria was reduced to 1.7 per 100,000 inhabitants, or only 750 deaths for the whole country. Morbidity was brought down to 61,000 cases, one-fourth the 1924 figure.

A part of the results obtained in these large fields of public health was due to the coördinated activities of organizations such as the Central Institute for Health, annexed by the Ministry of the Interior in Rome as a research and teaching center, and the National Fund for Maternal and Child Care (Opera Nazionale per la Maternita ed Infanzia). This National Fund for Maternal and Child Care was already planned when the fascists took over. It was developed during the regime of the fascists, who took all the credit. It still operates in the new Italian Republic of today. Its work was certainly important in helping to reduce infant mortality, possibly because it was effective in the fight against tuberculosis.

This is about all I can say in the short time that I have at my disposal about medicine in Italy under Fascism. A more complete analysis, garnished with more statistical data, would not change the general picture. And this is a sad panorama, dominated by a substantial contrast between claims of progress, for which the regime wanted the entire credit, and actual inertia—except, as I pointed out, in the field of public health.

Now it is proper to ask whether the credit for the work of rehabilitation in such a large field of public health as the fight against tuberculosis and malaria should go completely to fascism or whether it should not go also to those who conducted the campaign at the periphery, i.e., the doctors, the welfare associations, the volunteer workers, and so on. As I saw this job done, being in the midst of it from 1924 to 1938 in different capacities from that of a country doctor to that of a university professor, the work was done for the greatest part not for political reasons, fascist or otherwise. It represented the honest contribution of citizens willing to better conditions for the general welfare of their country. It proceeded from the devotion of the people to the cause of their fellows' betterment. It was also a response to a call of duty untinged by political ideology.

As a matter of fact, when the regime and its propagandists were proclaiming that infant mortality should be decreased and maternal

care bettered in order to save more lives so that more soldiers would be available for the empire, and when the fascists were shouting that better health was indispensable in the creation of stronger legions for the conquests to come, the people remained completely unimpressed.

From the moral point of view, one could say that the credit which goes to the fascist regime for having initiated or advanced the projects of public interest to which I have referred is in great part discounted by their proclaimed motives. Those projects were undertaken not for the good of the people but in order to achieve a political program of warlike expansion, which in the end could only lead to war—and it did.

Are we going to accept as valid the principle that in the 20th century the people of unified Italy could not have undertaken to plan the modernization of their medicine and public health without compulsion? And where is the proof that for that part of the program which was realized, the success was due to the adhesion of the people to the political ideology which was behind it? I am not afraid to say that it was not, and I am very confident that everyone who knows the Italian people well and was in Italy during the fascist regime, will be unable to contradict me.

Now I would like to call your attention (by way of parenthesis, but a very important one) to the fact that during the period of 1940 to 1943, and even 1944 and 1945 for the north of Italy, when the Germans were managing the political affairs of Italy, and the SS and the black shirts were scurrying around with increasing ferocity, shooting political adversaries and sending Jews and non-Jews in sealed cars to the extermination camps of Germany and Poland, one could look in vain for a single instance of participation of Italian medical men in such cruelties and brutalities, which we now know were perpetrated by their scientifically better known colleagues of Germany. We know instead of many instances of generous intervention of Italian doctors, who despite great personal danger, which was even greater when they belonged to the fascist party, accepted Jewish people in their hospitals and even in extreme cases performed fake operations on them in order to save those unfortunates from deportation and death.

In conclusion, my appraisal of the influence of fascism upon Italian medicine would be that it failed to modernize the practice and teaching of medicine; it was effective in encouraging some large enterprises in public health, which were promoted with wrong political motives;

and it failed to imbue the doctors with a philosophy which was repulsive to them. However, in spite of this last conclusion, I am not certain that some more durable damage was not done. If it was so, it of course did not affect the doctors alone; but the doctors, who have a peculiar function in human society, were apt to suffer more from it. Some 130 years ago the French philosopher and politician, Benjamin Constant, remarked that "When the people is only enslaved without being dispirited, there is for it a possibility for a better state of affairs; if some favorable circumstance will present itself, this people will make good use of it. Despotism allows this chance to humans. But usurpation dispirits the people at the same time that it oppresses them. Usurpation accustoms it to trample upon what it respected, to court what it disdains, and to disdain itself. It makes any liberation and amelioration impossible, even after it fails."

Here we have the key, I think, to that condition of depression, moral fatigue and incertitude in which I found the intellectuals of Italy and the doctors in particular, when I went back in 1945. I do not think that this situation is beyond remedy, as Constant was inclined to believe. What happened in Italy and in other countries dominated by a dictatorial regime should be a lesson for those who can profit from it. For those who were damaged by that disease and are still painfully recovering, all the sympathy of more fortunate peoples and some help are in order. This is already forthcoming and there is no reason to believe that it will not continue in a still more substantial way.

SECTION ON MICROBIOLOGY

JANUARY 19, 1949

I. EXECUTIVE SESSION
Reading of the Minutes

II. PAPERS OF THE EVENING

INSECTICIDES

a. Chemical aspects of some of the newer insecticides
H. L. Haller (by invitation)
U. S. Department of Agriculture
Washington, D. C.

b. The major toxic actions of insecticides
A. J. Lehman (by invitation)
Federal Security Agency, Food and Drug Administration,
Washington, D. C.

c. Recent advances in medical and veterinary entomology
E. F. Knipling (by invitation)
U. S. Department of Agriculture
Washington, D. C.

GREGORY SHWARTZMAN
Chairman

HARRY MOST
Secretary

Chemical Aspects of Some of the Newer Insecticides

H. L. HALLER

The use of chemicals to control injurious insects has been accorded more publicity during the past five years than in all the previous years during which research on insecticides has been carried out. This attention has been due in a large measure to the discovery of the outstanding insecticidal properties of several synthetic organic compounds, especially chlorinated hydrocarbons, such as DDT, benzene hexachloride, chlordane, and toxaphene (chlorinated camphene). More recently several organic phosphorus compounds have been found to be highly toxic to a wide range of insects. Several of the discoveries were made at a time when the need for better insecticides to control insect pests on food and fiber crops, stored products, livestock, and forest products was greater than ever before and when the available supply of the standard agricultural and household insecticides—pyrethrum, nicotine, rotenone, and the arsenicals—was unusually low. Although the findings may appear to some to be due to hastily initiated wartime research and largely fortuitous, this is not the case. Rather, the discoveries are the culmination of extensive explorations over a period of about 80 years. Chemicals have been used for a longer time to combat injurious insects but it is only since about 1867 that a systematic study to find new insecticides has been under way.

The early studies were concerned largely with inorganic compounds such as paris green and lead arsenate. By 1910 agricultural practices had become more intensified and insect populations increased, as did the losses which they caused to many important crops. About the same time investigators became interested in finding out how insecticides kill, and emphasized the importance of their physical characteristics, such as wetting and spreading of sprays, on

foliage and insects. A few years later studies were initiated to determine the chemical structures of the highly effective, naturally occurring plant insecticides, the pyrethrins and rotenone. These studies proved fruitful, and the structural formulas that were developed served as patterns for the preparation of organic compounds thought to be toxic to injurious insects. The studies were supplemented by the testing of a large number of synthetic organic compounds which became available soon after the first World War and for which a use was being sought. The two approaches have been profitable and have led to the discovery of a number of compounds highly toxic to insect pests.

The knowledge that an organic compound is highly toxic to several species of insects is not the only requirement for its immediate widescale use. Before its utility in controlling injurious insects can be determined, information must be obtained as to the safety of the chemical to public health, to farm animals, to soils, to vegetation, to beneficial insects including bees, and to wildlife wherever these interests are involved. It is necessary to know the range of effectiveness (that is, to what kinds of insects the product is toxic); the stage of the insect that is destroyed (egg, larva, or adult). Such studies are the joint affair of biologists and chemists.

Few, if any, of the newer insecticidal chemicals are suitable for use as insecticides in the undiluted form. Aside from the fact that it would be uneconomical for most purposes to use potent agents without diluting them greatly, the physical properties of the substances usually are such that they are unsuited for direct application. To determine whether the compound can best be applied as a dust, spray, or as an aerosol a knowledge of the physical and chemical characteristics of the product is needed. Physical and chemical studies should include determination of the composition of the product, its solubility in various solvents, and its compatibility with other insecticides, fungicides, and dust diluents. Methods for the analysis of the product itself, as well as in dusts, in sprays, and in combination with other insecticides, must be developed. Procedures for determining the product as a spray residue are also needed.

As the time allotted to me will not permit the discussion of all of the newer insecticides I shall confine my talk to the chemistry of some of the more important chlorinated hydrocarbons and the organic phosphorus compounds.

The chlorinated hydrocarbons that have attracted most attention are DDT, TDE (also known as DDD), methoxychlor (methoxy analog of DDT), benzene hexachloride, toxaphene (chlorinated camphene), and chlordane. Although methoxychlor contains oxygen it is included because of its close relationship to DDT. The technical grades of all six of these products are mixtures of two or more isomeric compounds, the relative insecticidal value of which varies with the product and the test insect. The empirical formula and the total chlorine content of each is given in Table I.

These products possess one common chemical characteristic to which their outstanding insecticidal property has been attributed. In the presence of alcoholic alkali and in some cases with traces of certain metals, such as iron, aluminum and others they lose one or more moles of hydrogen chloride. If this reaction is a factor in making them toxic to insects it is only a minor one as many related compounds are known which likewise yield

TABLE I.

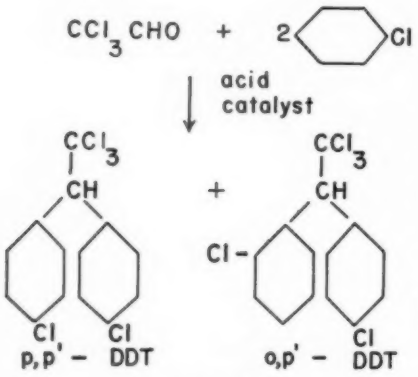
FORMULA AND CHLORINE CONTENT OF SOME CHLORINATED HYDROCARBON INSECTICIDES

Product	*Formula*	*% Chlorine*
DDT	$C_{14}H_9Cl_5$	50.01
TDE	$C_{14}H_{10}Cl_4$	44.33
Methoxychlor	$C_{16}H_{15}O_2Cl_3$	30.77
Benzene hexachloride	$C_6H_6Cl_6$	73.15
Chlordane	$C_{10}H_6Cl_8$	69.22
Toxaphene (chlorinated camphene)	$C_{10}H_{10}Cl_8$	68.54

hydrogen chloride but are relatively non-toxic to insects. The speed at which the hydrogen chloride is released from the compound is not a vital factor either because DDT yields it quite rapidly whereas the methoxy analog of DDT does not.[1] Our knowledge of the relationship between insecticidal action and chemical constitution is too limited to state that any one reaction will determine whether a compound possesses insecticidal properties.

DDT

The studies leading to the discovery of DDT as an insecticide are presented in detail by Läuger, Martin and Müller.[2] The symbol DDT is a contraction for Dichloro-Diphenyl-Trichloroethane. However, the term DDT has been confined to the product obtained on condensation of chloral with chlorobenzene in the presence of sulfuric acid. The chemistry of DDT has been investigated more extensively than that of the other chlorinated hydrocarbons.[3] Formula I illustrates the formation of DDT.



Formula I

When pure chloral and pure chlorobenzene are used the reaction product consists essentially of two isomeric compounds, p,p'-DDT and the o,p'-DDT. Technical DDT contains approximately 3 to 4 parts of the former isomer to one part of the latter.

The toxicity of these two isomers to several insects is shown in Table II.

TABLE II.

COMPARATIVE TOXICITY OF P,P'-O,P'-DDT TO VARIOUS INSECTS*

	p,p'-DDT		*o,p'-DDT*	
Insect	*Concentration* %	*Kill* %	*Concentration* %	*Kill* %
Houseflies	1.0	70	5.0	1
Body lice	0.05	100	1.0	0
Mosquitoes†				
Adults	0.5	49	5.0	23
Larvae	0.0015 (p.p.m.)	50	0.011 (p.p.m.)	50

* These results were obtained at the Orlando, Fla., laboratory of the Bureau of Entomology and Plant Quarantine.

† *Anopheles quadrimaculatus* Say.

It will be noted that although the o,p'-DDT is practically non-toxic to the adult form of these insects it is a very effective compound against mosquito larvae. This specificity manifests itself with many of the synthetic organic compounds.

It is natural to inquire as to the effect of replacing one or more chlorine atoms in DDT in both the benzene rings and the ethane part of the molecule with other atoms or radicals. Such compounds have been synthetized but more work has been done with analogs in which the chlorine atoms of the benzene rings have been replaced than with compounds in which the chlorine atoms in the ethane molecule have been substituted.

The toxicity of some analogs of DDT to mosquito larvae is given in Table III.

It is of interest to note that the replacement of chlorine atoms in the benzene ring by the hydroxyl radical gives a product that is relatively non-toxic. Methylation of the free hydroxyl group produces a potent insecticide. The product obtained with the methyl radical in place of chlorine is effective but that with the tertiary butyl group is of little value as an insecticide. Similar results were obtained when these

TABLE III.

TOXICITY TO FOURTH-INSTAR LARVAE OF ANOPHELES QUADRIMACULATUS OF DDT ANALOGS IN WHICH CHLORINE ATOMS IN BENZENE RINGS HAVE BEEN REPLACED WITH OTHER ATOMS OR RADICALS*

Substituents on Diphenyltrichloroethane	*Dosage, P.P.M.*	*% Mortality after 48 Hr.*
p,p′-di-Cl (DDT)	0.005	100
p,p′-di-Br	0.005	100
p,p′-di-F	0.01	85
p,p′-di-CH_3O	0.01	100
p,p′-di-OH	10	20
p,p′-di-H	0.1	25
p,p′-di-CH_3	0.01	100
p,p′-di-tert-Butyl	10	20
p,p′-Cl,H	0.01	85

* Deonier, C. C., Jones, H. A., Haller, H. L., Hinchey, E., and Incho, H. H., *Soap and Sanitary Chemicals*, 1946, *22*:118.

compounds were tested against a number of agricultural insect pests.[4,5]

Although p,p′-DDT is effective against a wider range of injurious insects than most of the other synthetic organic insecticides so far tested, it is not a panacea for all ills due to insects. DDT has little or no effect on the boll weevil, the cotton leafworm, the cotton aphid, the Mexican bean beetle, red spiders, cattle grubs, adults of the Florida and California red scales, the sugar-cane borer, orchard mites, the parlatoria date scale, and the plum curculio. It is effective against some aphids but as a rule is less effective than nicotine. It has also registered failures for one reason or another against the tobacco hornworm, the cabbage seedpod weevil, the tomato russet mite, etc.

METHOXYCHLOR

Methoxychlor is the coined name adopted for the methoxy analog of DDT, 1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane. The technical product is obtained on condensation of chloral and anisole.[6] Methoxychlor is effective against numerous agricultural insect pests, including the Mexican bean beetle, and has been reported[7] to give a more rapid "knockdown" of flies than DDT.

TDE (DDD)

TDE also called DDD is the symbol for *d*ichloro *d*iphenyl *d*ichloroethane, a *t*etra chloro *d*iphenyl *e*thane. *p,p′*-TDE is 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane. TDE is obtained on condensation of dichloroacetaldehyde and chlorobenzene.[8] The *p,p′*-TDE is equal in toxicity to *p,p′*-DDT against mosquito larvae[9] and closely parallels DDT in effectiveness against both household and agricultural insect pests.[8]

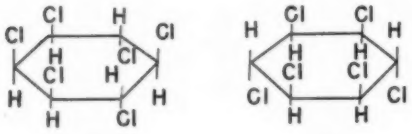
BENZENE HEXACHLORIDE

The insecticidal properties of benzene hexachloride or 1,2,3,4,5,6-hexachlorocyclohexane were discovered independently about the same time in France[10] and England[11] during World War II while there was no communication between the two countries.

It is of interest that benzene hexachloride $C_6H_6Cl_6$ is insecticidal whereas hexachlorobenzene, C_6Cl_6 has no insecticidal properties.

Benzene hexachloride is prepared by the addition of chlorine to benzene in the presence of actinic light.[12] The reactants are required in the ratio of 3 moles of chlorine to one mole of benzene. It has not yet been possible to add chlorine to the three double bonds stepwise, that is, with the formation of dichloro or tetrachloro derivatives. When the ratio is other than three to one, the final product under all conditions so far tried, is a mixture of unchanged benzene and benzene hexachloride. The reaction product consists of a mixture from which five isomeric benzene hexachlorides have been isolated. These have been designated as alpha, beta, gamma, delta, and epsilon isomers. Their alphabetical designations indicate the order in which they have been discovered and described in the literature and bear no relation to their relative structures. Of these isomers only one, the gamma isomer, which occurs to the extent of 10-12 per cent in technical benzene hexachloride, has outstanding insecticidal properties.

The formation of the isomers may be explained in the following manner. If it is assumed that all of the carbon atoms of the cyclohexane ring lie in one plane eight stereoisomers of hexachlorocyclohexane, one of which exists in mirror-image form, are theoretically possible. The configuration shown in Formula IIa was originally assigned to the gamma isomer. This configuration has recently been shown to be incorrect and the isomer may be more nearly correctly represented by Formula IIb.[13]



A B

Formula II

Benzene hexachloride is toxic to a wide range of agricultural insect pests, especially the cotton boll weevil against which DDT is ineffective. The technical product has a musty persistent odor which may limit its usefulness for certain purposes.

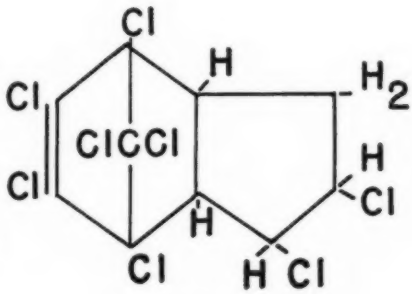
Table IV shows the toxicity of each of four isomers to mosquito larvae. Like p,p'-DDT, the gamma isomer is slow in its killing action and does not cause "knockdown." At the time that these tests were made the epsilon isomer was not available.

TABLE IV—TOXICITY OF VARIOUS ISOMERS OF BENZENE HEXACHLORIDE TO LARVAE OF ANOPHELES QUADRIMACULATUS

Isomer	*Dosage P.p.m.*	*Mortality in 24 Hours Percent*	*Mortality in 48 Hours Percent*
Alpha	2.5	88	92
Beta	100	22	40
Gamma	.01	80	100
Delta	2.5	40	62
DDT	.01	98	100
	.005	53	85

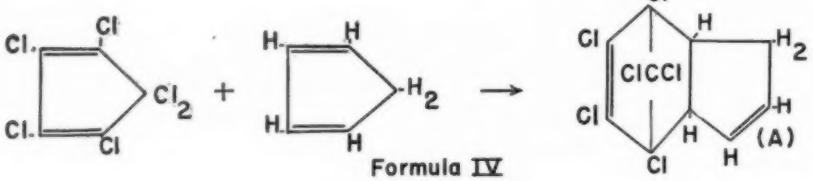
CHLORDANE

Chlordane is the common name assigned to the compound designated as 1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a,4,7,7a-tetra-hydroindan and having the structure shown in Formula III.



Formula III

It is prepared by allowing hexachlorocyclopentadiene and cyclopentadiene to react as shown in Formula IV.



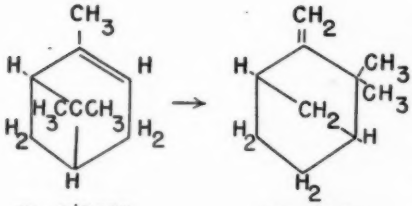
Formula IV

The adduct IV, dissolved in a suitable solvent, such as carbon tetrachloride, is treated with chlorine gas with the resultant addition of 2 atoms of chlorine to the double bond (A) to form chlordane (III).[14] Technical chlordane contains 60-75 per cent of chlordane, the remainder being closely related compounds that occur in the normal process of manufacture and which are toxic to insects. Chlordane has been found to be toxic to a wide range of agricultural and

household insect pests.[15] It is especially effective against grasshoppers and cockroaches and it has considerable residual effectiveness.

TOXAPHENE (CHLORINATED CAMPHENE)

Another chlorinated hydrocarbon with outstanding insecticidal properties is found among the terpene derivatives. The product was originally designated a chlorinated bicyclic terpene.[16] Subsequently the coined name chlorinated camphene was developed for it. More recently this has been changed to toxaphene by which the technical product is now known. By the chlorination of camphene, which is obtained by the isomerization of pinene from pine wood extract, to a chlorine content of 67-69 per cent a product is obtained which has the approximate empirical formula $C_{10}H_{10}Cl_8$. The probable method of formation is given in Formula V although the exact structure is not known.



Formula V

Toxaphene has been found toxic to a considerable number of agricultural insect pests, especially grasshoppers and insects attacking cattle.

ORGANIC PHOSPHORUS COMPOUNDS

Three organic phosphorus-containing compounds, hexaethyl tetraphosphate, tetraethyl pyrophosphate, and parathion have received considerable attention for the control of injurious insects. Hexaethyl tetraphosphate is the name given by a German investigator to a product obtained by allowing triethyl orthophosphate to react with phosphorus oxychloride as shown in Formula VI.

$$3(C_2H_5)_3PO_4 + POCl_3 \rightarrow (C_2H_5)_6P_4O_{13} + 3C_2H_5Cl$$

Formula VI

Essentially the same reaction product is obtained from triethyl orthophosphate and phosphorus pentoxide as indicated in Formula VII.

$$2(C_2H_5)_3PO_4 + P_2O_5 \rightarrow (C_2H_5)_6P_4O_{13}$$

Formula VII

Chemical examination of hexaethyl tetraphosphate has shown it to be a mixture containing as its principal active ingredient the compound tetraethyl pyrophosphate. Other constituents are ethyl metaphosphate and triethyl orthophosphate, both of which are relatively insecticidally inactive materials. Pentaethyl triphosphate, an unstable ester possessing insecticidal properties, may also be present but this has not been established with certainty.

As produced by either of the reactions above tetraethyl pyrophosphate is present to the extent of about 15-20 per cent. Modification of either process by increasing the proportion of the triethyl orthophosphate results in a product of empirical formula $(C_2H_5)_4P_2O_7$ which is an even more potent insecticide than hexaethyl tetraphosphate. The reaction is shown in Formula VIII.

$$5(C_2H_5)_3PO_4 + POCl_3 \rightarrow 3(C_2H_5)_4P_2O_7 + 3C_2H_5Cl$$

$$4(C_2H_5)_3PO_4 + P_2O_5 \rightarrow 3(C_2H_5)_4P_2O_7$$

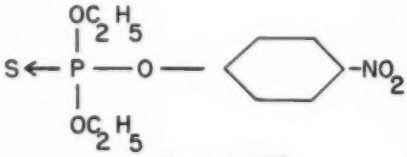
Formula VIII

The reaction products are not pure tetraethyl pyrophosphate but are mixtures of ethyl phosphates and polyphosphates containing approximately 40 per cent of this principal active ingredient.

German chemists had reported that in water solution or in the presence of atmospheric moisture hexaethyl tetraphosphate was completely hydrolyzed in 24 hours to ethyl alcohol and orthophosphoric acid. Hall and Jacobson[17] in a study of the hydrolysis of hexaethyl tetraphosphate, however, found that although rapid hydrolysis to non-insecticidal products occurs, the end-products are monoethyl and diethyl orthophosphoric acid. Pure tetraethyl pyrophosphate hydrolyzes to diethyl orthophosphoric acid. This rapid hydrolysis to non-toxic products greatly limits the duration of the insecticidal effectiveness of tetraethyl pyrophosphate but it also eliminates the danger of toxic residues on the crops treated.

Both hexaethyl tetraphosphate and tetraethyl pyrophosphate are especially useful against mites and such soft-bodied insect pests as aphids, mealy bugs, and thrips. Both compounds have been shown to inhibit the action of cholinesterase[18] and acetyl esterase.[19]

Another phosphorus-containing organic insecticide is O,O-diethyl O-p-nitro-phenyl thiophosphate Formula IX to which the coined name parathion has been assigned.



Formula IX

This insecticide also was discovered in Germany during World War II where it was designated E-605.[20, 21]

According to Thurston[21] the product is obtained by the following sequence of reactions: "Phosphorus trichloride is combined with sulfur by heating at 130°C. for two hours in a lead-lined autoclave. A quantitative yield of phosphorus thiotrichloride is obtained. The soluble sulfur compounds are removed by distilling the product from a lead-lined kettle. The resulting product boils at 125°/760 mm. pressure. This material is then combined with sodium ethoxide contained as a 10 per cent solution in alcohol. The formed diethoxythio-phosphorous chloride is poured into water and decanted. This intermediate product is stable in water and alcohol and only slowly decomposes when heated with them at temperatures of 80-90°C. Sodium p-nitrophenate in chlorobenzene is then combined with the diethoxy-thiophosphorous chloride by heating at 130°C. The finished product is not distilled, only the chlorobenzene, which is used as the reaction medium, is removed. The yield of the crude product is 80-90 per cent, since the formation of phosphorous thiotrichloride is quantitative (sic) and the remainder of the reactions are very good."

Parathion is an oily liquid with a disagreeable garlicky odor. It has a low vapor pressure of 0.0006 mm. of mercury at 24° and can be distilled only under greatly reduced pressure. It is not hydrolyzed appreciably in neutral water but is hydrolyzed in alkaline waters. It has proved highly toxic to all of a wide range of insects against which it has been tested. Since it is relatively stable, its effectiveness persists for a considerable time, reportedly from a few days to several weeks.

Both tetraethyl pyrophosphate and parathion are highly toxic to warm-blooded animals.[22] They are absorbed through the skin and extreme care must be taken in using them. Moreover, in the case of parathion because of its greater stability there is the possibility of toxic residues from its application.

SUMMARY

Although much progress has been made in the development of new materials for combating insect pests many problems must be solved before their utility as practical control measures is determined. It is necessary to know against what kinds of insects the product is effective, the stage at which the insect is most susceptible—egg, larva, or adult—and the compatibility of the material with solvents, carriers, fungicides, or other insecticides. It must also be determined whether the material can be applied best as a dust, a spray or an aerosol and whether it causes plant injury when applied either to the foliage or to the soil. Its effect on

beneficial insects, such as bees and various parasites and predators, and its toxicity to warm-blooded animals, especially man, must also be ascertained. These and many other factors need to be established before a new product finds full use in the field of economic entomology.

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(*Section on Microbiology continued on next page*)

The Major Toxic Actions of Insecticides

ARNOLD J. LEHMAN

This review is an attempt to summarize the more important toxicological features of the commonly used insecticides. It should be stated at the outset that thousands of formulations involving probably not more than 25 insecticides are in existence. The solvents, diluents, and wetting agents which compose these formulations have some bearing on the toxic phenomena exhibited by the insecticides. In a good many instances these "inert ingredients" may be solely responsible for the injuries and it is not always possible to state definitely which of the ingredients should be incriminated. In the interest of accuracy, and to eliminate the side effects of the "inert ingredients," the toxic manifestations as given below for experimental animals were observed following the oral administration of poisons of high purity, either as such or in an innocuous solvent. It is impossible to state the fatal dose in humans for many of these insecticides and such doses can only be estimated from animal experimentation.

INSECTICIDES FROM VEGETABLE SOURCES

DERRIS

The insecticidal quality of this plant is due to a number of constituents but principally rotenone.

Local effects. Rotenone, when applied to the skin, produces only an occasional mild irritation which persists about 24 hours after removal of the causative agent. Irritation of the conjunctiva may result on contact but no permanent damage has been reported. Rotenone is not absorbed by the skin.

Symptoms. The most pronounced effect of rotenone is upon resipration which is first stimulated and then depressed. If a sublethal dose has been ingested, stupor may be evident, and frequent convulsive seizures may be observed. Death is invariably the result of respiratory failure since the heart and blood pressure may be maintained for some time after cessation of respiration. The cardiovascular system is not seriously affected even after massive doses of derris or its constituents.

Fatal dose. This is probably quite large, although guinea pigs do not survive after 60 mg./kg. dose administered orally. Dogs have tolerated as much as 2.0 gm./kg. It has been shown experimentally that finely powdered rotenone is about six times as poisonous as coarse crystals. Further, the intravenous toxicity of rotenone is 3,000 to 8,000 times the oral toxicity. When it is called to mind that the inhalation of finely divided substances produces effects of about the same order as those observed following intravenous administration, it can be seen that the inhalation of finely powdered rotenone or derris can become a very serious matter.

Fatal period. The onset of symptoms of poisoning may appear within a few minutes to a few hours, depending on the dose. Death can occur as early as 4 hours after ingestion of the poison or may be delayed for as long as 10 days with the crucial period falling between the first and second day.

Pathology. Pathological changes are almost always the result of chronic ingestion. A definite necrosis of cells in the central and midlobular areas of the liver has been a constant observation in chronically poisoned animals. Concentrations of derris root in the neighborhood of 75 parts per million in the diet have been reported as having produced these changes. This represents about 3.75 parts per million of rotenone. It has been estimated that the upper limit of tolerance for man is about 5 parts per million of derris in a diet consisting wholly of derris-contaminated food.

Treatment. Since rotenone acts as a gastric irritant and also stimulates the emetic center after absorption, these two factors operate to remove the swallowed material before serious poisoning occurs. No specific antidotes are known and treatment must be symptomatic.

PYRETHRUM

The active constituents are called pyrethrins. The pure substances are rare and the highest concentrations which may be encountered in commerce are 20 per cent pyrethrum extracts in soy bean or sesame oil.

Local effects. The pyrethrins are slightly sternutatory and possess an acrid bitter taste which is followed by a numbness of the tongue and lips. Highly concentrated extracts have been applied to human skin without signs or symptoms of irritation.

Symptoms. The pyrethrins produce a hyperexcitability. Incoordination, tremors, and muscular paralysis have been noted with death due to respiratory paralysis.

Fatal dose and period. The single acute oral dose is quite large in animals, being of the order of 1.5 gm./kg. Poisoned animals may die within 10 hours or may live 3 to 5 days or longer before succumbing.

Pathology. The toxicity of the pyrethrins appears to be so slight in warm-blooded animals that no tissue damage has been reported as caused by these agents. Allergic reactions and contact dermatitis have been reported in humans.

Treatment. Since household preparations contain the equivalent of about 108 mg. of pyrethrins per 100 cc. of kerosene, any toxic effects following the inadvertent swallowing of this solution would be due to the ingested kerosene. Gastric lavage is about all that can be recommended.

NICOTINE

This is one of the very few volatile, liquid alkaloids. It unites with acid to form water-soluble salts, the form in which it appears on the market.

Local effects. Tobacco and nicotine are strong local irritants. Nicotine penetrates the skin readily but its salts do not; hence strong solutions of the latter may be spilled on the skin without serious consequences.

Symptoms. Nicotine is one of the most rapid and deadly poisons known to man. The initial hot, burning sensation in the mouth, esophagus and stomach is followed by salivation, nausea and vomiting. Convulsion appears later which may be clonic and tonic in nature. Death is due to a curare-like paralysis of the respiratory muscles.

Fatal dose and period. About 60 mg. as a single dose appears to be the smallest quantity which can be fatal to man. It has been estimated that a 70-kilo individual can ingest a total of 280 mg. of nicotine daily in the form of tobacco without harm. The effects of chronic poisoning are those of inanition.

Treatment. There is no specific antidote for nicotine. Stomach lavage with tannic acid (strong tea or coffee), administration of charcoal or permanganate are aids in removing and destroying the poison. Artificial respiration is one of the most important life-saving measures and should be instituted as soon as respiratory collapse is apparent.

SYNTHETIC INSECTICIDES

LETHANES

These constitute a group of insecticides based on aliphatic thiocyanates, four of which have attained commercial importance.

Local effects. The local effects of solutions of the lethanes are due primarily to the vehicle (refined kerosene) in which they are dissolved. The concentrations of 2 or 3 per cent of active ingredient as ordinarily used are not high enough to cause skin irritation.

Symptoms. The symptoms are a deep depression, cyanosis, dyspnea, and tonic convulsions. Death is due to respiratory failure.

Fatal dose. Since the highest concentrations of the individual lethanes which may be encountered are 50 per cent solutions in kerosene, the additive effect of this solvent must be taken into account. A rough estimate would be 0.4 to 2 cc./kg. of the concentrates, with lethane-384 represented by the lower figure and thanite by the higher figure. Lethane-60 and lethane-384 special fall between these two extremes.

Fatal period. Fatal doses of the thiocyanates produce a rapid collapse and death within a few minutes. Occasionally, toxic effects are delayed for as long as 12 hours.

Pathology. No characteristic changes in tissues have been noted. The severe circulatory disturbances which the thiocyanates produce cause a marked hyperemia of the internal organs, hemorrhages, and edema. Degenerative changes in the brain, liver and kidney have been reported in chronically

poisoned animals.

Treatment. There is no specific treatment for poisoning by the thiocyanates. Removal of the poison from the gastrointestinal tract by the usual methods and treatment of symptoms as they arise are advised. Poisoning by these agents is an "all or none" phenomenon. If an individual survives the acute effects, recovery is practically assured.

DDT and Its Analogs

There are three members in this group, namely, DDT, methoxychlor, and TDE.

DDT

Local action. DDT is quite innocuous when applied to the skin. Solutions of DDT, however, are absorbed and multiple exposures do constitute a hazard. It has been estimated that daily exposures to solutions representing 9 grams of DDT, by spilling on the skin or clothing, may represent a quantity dangerous to man.

Symptoms. The symptoms of poisoning in mammals usually begin as tremors of the muscles of the head and neck. The tremors progress caudally and increase in intensity with time so that eventually purposeful movements are difficult or cannot be accomplished. Frequent episodes of tonic and clonic convulsive seizures manifest themselves. These convulsive seizures occur with increasing frequency, becoming almost continuous. A stage of depression is eventually reached, terminating in respiratory failure and death. An uncomplicated case of poisoning in man has not been reported, but from the meager information available it appears that giddiness, nervous tension and involuntary muscular tremors are some of the symptoms.

Fatal period. The onset of poisoning symptoms after oral ingestion of DDT may be delayed for several hours but can appear in one hour. The convulsive seizures are manifest within 30 or 40 minutes after the onset of tremors and death may occur 2 to 24 hours after the onset of the initial tremors.

Fatal dose. The fatal dose of DDT for man is not known. One report of a fatal case of poisoning estimates the dose as 500 mg./kg., representing about an ounce total dose of the solid material.

Pathology. The gross pathologic changes induced by DDT are not significant except in chronically poisoned animals. The outstanding lesions are found in the liver. Lighter grades of poisoning reveal a moderate degree of centrolobular hypertrophy of the hepatic cells, progressing to a combination of central necrosis and reparative hypertrophy in some cases of more severe intoxication. Some cerebellar changes of a degenerative nature have been observed in dogs. There is also a tendency to hepatic cell tumor formation in animals on long-term chronic ingestion of DDT.

Treatment. Treatment of acute poisoning should be directed toward removal of the DDT from the stomach and intestinal tract. Oil cathartics must be avoided. The chemical stability of DDT precludes the use of chemical antidotes. The neurological manifestations may be treated with an anticonvulsant drug, the best physiological antidote being phenobarbital. Enough should be given to control the tremors and convulsions. Experiments indicate that this dose is well below the anesthetic dose. DDT produces an excess excitability of the cardiac muscle so that any coincident sympathetic stimulation which accompanies the emotional disturbance induced by DDT convulsions can result in ventricular fibrillation. This can also be induced by a challenge dose of epinephrine which is, therefore, contraindicated in the treatment regimen.

Methoxychlor

Local effect. Methoxychlor is only slightly irritating when applied to the skin. Solutions of the compound are absorbed by the skin, and multiple exposure to oil solutions representing about 36 grams daily can be dangerous to man.

Symptoms. Symptoms from a single acute dose of methoxychlor may not appear, since the quantities which must be ingested to produce toxic effects are so large it is rather doubtful whether an individual would swallow enough to cause poisoning. When symptoms do appear they are largely limited to a depression, although tremors have been noted in chronically poisoned animals.

Fatal dose and period. The fatal dose for

man is estimated to be in the neighborhood of 450 grams (1 pound) if ingested at one time. Onset of symptoms begins in about 24 hours but may not be evident for 72 hours. Death when it does occur is between 2 and 4 days after ingestion of the poison.

Pathology. Pathologic changes are seen only after subacute feedings of the poison at high levels in the diet (5000 parts per million) and are predominantly centered in the kidney. The damage consists of glomerular and tubular atrophy scattered diffusely throughout the organ.

Treatment. Probably little harm will be done if the material is swallowed. Removal of the insecticide from the stomach and intestinal tract is about all that should be necessary. Oil cathartics should be avoided.

TDE

Local effect. It is slightly irritating to the skin. Multiple exposures to oil solutions and the daily contact with quantities of about 6 grams total may be considered as the upper limit of tolerance for man.

Symptoms. The symptoms of TDE poisoning fall into the category of lethargy. Careful observations have not revealed convulsions, although these can be elicited by administering the poison intravenously.

Fatal dose and period. The fatal dose of TDE is about 10 times larger than that of DDT, which would place the total quantity at about 8-10 ounces of the solid material. The first symptoms of poisoning occur within 24 hours, with death within 48-96 hours after ingestion. Animals which survive after the 96th hour usually recover completely.

Pathology. TDE shows a predilection for the adrenal cortex, which may be briefly described as a marked chronic atrophy of the cortex. As with all chlorinated hydrocarbons, the liver shows damage similar to that described under DDT.

Treatment. This is the same as that given under methoxychlor.

Other Chlorinated Hydrocarbons

CHLORDANE

This insecticide is composed of several isomers and the true evaluation of its toxicology can only be made after each of the isomers has been subjected to study. The comments below deal with the commercial products.

Local effects. Chlordane is moderately irritating to the skin. This property is lost on dilution, as in insecticide formulations, and the warning sign of danger is lost. The insecticide is absorbed through the skin, and it has been estimated that daily exposure to about 2.4 grams in solution may be dangerous to man.

Symptoms. The early signs are those of irritability of the central nervous system. This leads eventually into convulsions, which are followed by a period of depression. The process may be repeated several times, and death follows a terminal deep depression with or without a final convulsive seizure.

Fatal dose. From the acute standpoint chlordane appears to be only about one-half as poisonous as DDT, but the side effects are such that in the final analysis the toxicity is about 5 times that of DDT. Therefore, the fatal dose lies somewhere between 6 and 60 grams.

Fatal period. The onset of symptoms is within 45 minutes after ingestion. Deaths occur occasionally within 24 hours, are frequent between the 48th and 96th hour, and if survival extends to the 6th day, recovery is the rule.

Pathology. Inanition is a predominant observation in chronic poisoning, indicating a considerable disturbance in normal physiology. Of the vital organs, the liver bears the brunt of the poisoning, and the usual degenerative changes produced by chlorinated hydrocarbons are a constant finding.

Treatment. The usual measures should be adopted for removing the poison from the stomach and intestinal tract. Any additional treatment must be symptomatic as no specific antidotes are known.

BENZENE HEXACHLORIDE

The commercial product contains at least 4 isomers, each contributing to or modifying the effects of one on the other when administered in combination.

Local effects. The technical grades of benzene hexachloride (containing the 4 isomers, alpha, beta, gamma, and delta in varying proportions) are skin irritants, the damage being almost in direct proportion to the

amount of gamma isomer these mixtures contain. Toxic effects can be elicited by dermal application, and again the gamma isomer plays the leading role. The toxicity of this isomer increases 200 fold on repeated exposure, and dangerous quantities to man are probably of the order of a little more than 1 gram if repeated daily.

Symptoms. Animals which are poisoned with technical benzene hexachloride exhibit convulsions in some instances. This is followed by a hyperirritability to any outside stimulus (sudden noise, tapping the cage, etc.) and finally depression. When the symptoms of poisoning by the individual isomers are considered, the following facts are known.

Alpha induces a state of hyperexcitability which may develop into convulsions by any sudden stimulus.

Beta does not produce symptoms of poisoning from a single acute dose. If administered chronically, only tremors predominate at first but finally depression occurs and not unlike that observed with phenobarbital.

Gamma is a central nervous stimulant, the principal symptom being convulsions.

Delta acts as a depressant to the central nervous system.

Fatal quantity. Because the delta isomer is almost purely depressant in its effects, this component of the technical mixture has a tendency to antidote the stimulant actions of the other three components. This gives a rather wide range of dosage which may be fatal. Probably the best estimate for man would be 400 mg./kg. or about one ounce of technical benzene hexachloride containing 15 per cent gamma. Of the four isomers, Gamma may be met with frequently. The fatal dose is about one-half that of DDT and for man the fatal dose could be about 15 grams (one-half ounce) of the pure material.

Fatal period. The symptoms of technical benzene hexachloride poisoning begin within 1-2 hours after oral administration. The course of the fatal poisoning is not very rapid and death may be delayed for as long as 5 days. Gamma isomer is much more rapid in its action, the onset of symptoms developing within 30 minutes and death occurring within 24 hours, and rarely delayed beyond this time period. Since 50-70 per cent of the technical benzene hexachloride is composed of the alpha isomer, it may be worthwhile mentioning that symptoms of poisoning of this isomer begin in about 24 to 48 hours and death may be delayed for 4 or more days.

Pathology. In a general way, benzene hexachloride isomers gave a pathological picture resembling that caused by DDT. Liver damage is the characteristic finding. Alpha and gamma isomers cause a moderate degree of hyaline granular degeneration of the renal convoluted tubular epithelium.

Treatment. There are no specific antidotes for benzene hexachloride, and treatment should follow the general plans given under DDT.

TOXAPHENE

This is a chlorinated derivative of camphene.

Local action. Toxaphene is moderately irritating to the skin. Absorption through the skin has been observed experimentally and the quantity which may be dangerous to man by daily contact has been estimated at 2.4 grams.

Symptoms. Toxaphene, being a derivative of a camphor-like substance, elicits responses quite similar to camphor. Epileptiform convulsions are a prominent feature.

Fatal dose. Toxaphene is about 4 times as toxic as DDT. The fatal dose for man may be estimated to be about 2-7 grams or a maximum of one-fourth ounce.

Fatal period. In poisoned animals toxic symptoms appear within an hour, with death following usually within 4 hours, or may be delayed for 24 hours.

Pathology. The major pathologic damage is located in the liver and does not differ much from the changes given under DDT.

Treatment. Evacuation of the stomach and bowels is indicated. Experimentally, the convulsions can be controlled by phenobarbital. Bromides are useful in controlling camphor convulsions and this probably also applies to toxaphene.

ORGANIC PHOSPHATES

There are two important members in this group, namely, tetraethyl pyrophosphate and

parathion. The toxic manifestations of these compounds are similar, but the mechanism of their poisonous action is considerably different from that described above for the other insecticides.

Local action. The organic phosphates are only slightly irritating to the skin. Both compounds penetrate the skin readily in all types of formulations. As little as 0.3 gram daily exposure has been estimated as dangerous to man.

Symptoms. The toxic manifestations of these two compounds are similar, the mechanism of their poisonous action being that of a cholinesterase inhibitor. The organic phosphates affect the postganglionic cholinergic nerves, that is, the nerves supplying smooth muscles and glands. This action has been termed the muscarinic effect. This action would manifest itself in man as follows:

a. Lacrimation.
b. Salivation.
c. Sweating.
d. Symptoms referable to the gastrointestinal tract, i.e., nausea, vomiting, diarrhea.
e. Respiratory distress as the result of bronchiolar constriction. These symptoms may be exaggerated in individuals with asthmatic tendencies.
f. Miosis and disturbance of vision.

The organic phosphates affect also the preganglionic and somatic motor nerves. This phase of their action is termed the nicotinic effect. The symptoms this action could produce may be listed as follows:

a. Flushing of the skin.
b. Throbbing in the head.
c. Effects on the blood pressure.
d. Various grades of heart block.
e. Muscular tremors of peripheral origin.

To what extent convulsions enter the picture is problematical. All evidence points to the conclusion that the cerebral motor cortex is not involved. Convulsions, if they should occur, may be of asphyxial origin and not as the result of a direct action of the organic phosphates.

Fatal dose. The organic phosphates are from 3 to 5 times as toxic as nicotine. Since the fatal dose for nicotine is estimated as 60 milligrams (1 grain), 12 to 20 milligrams (1/5 to ⅓ grain) of parathion or tetraethyl pyrophosphate may be considered as a poisonous quantity and liable to prove fatal. As little as 0.05 cc. (1 small drop) of the concentrated materials splashed into the eye may be fatal.

Fatal period. Onset of symptoms and time of death depend somewhat on the quantity ingested. In a general way, toxic effects make their appearance within 30 minutes, and death in the majority of fatal poisonings occurs between 1½ and 4 hours.

Pathology. In acute poisonings little of note is observed. In chronically poisoned animals enterocolitis and necrosis of the gall bladder are the predominant injuries.

Treatment. The usual measures for removal of the poison from the stomach and intestinal tract are recommended. Atropine sulfate is a physiological antidote for the muscarinic effect of the organic phosphates. Most of the first group of symptoms listed above would be alleviated by a 0.5 to 1.0 mg. dose. Whether or not this dose should be repeated would depend on the response of the patient. The development of mydriasis and dry mouth and throat is an indication that enough atropine has been given, and nothing could be gained by administering more of the drug.

Atropine does not antidote the nicotinic action of the organic phosphates. Peripheral muscular depressants appear to be of some value for controlling the tremors. Curare has this effect, but the therapeutic margin is quite narrow. The parenteral administration of magnesium sulfate may be a better choice. When magnesium is given parenterally one must guard against respiratory failure. Calcium successfully counteracts this action and it is therefore advisable that a solution of calcium chloride or gluconate for intravenous administration be available should the magnesium dosage be exceeded.

INSECTICIDE ACTIVATORS

This includes a group of compounds which will enhance the insecticidal effect of derris and pyrethrum. Two compounds, N-propyl isome and piperonyl butoxide, are of commercial importance at present.

These compounds are relatively inactive pharmacologically. The quantities necessary to produce poisoning are quite large, being of the order of 10-12 grams per kg., so that the hazards from ingesting a single dose of these materials appear to be of minor importance.

Recent Advances in Medical and Veterinary Entomology[1]

E. F. KNIPLING

Arthropods which attack man and animals affect directly or indirectly the lives of every individual in the world. The hundreds of species involved include vectors of important diseases such as malaria, typhus, bubonic plague, yellow fever, and many others, which have plagued mankind with devastating epidemics during the past. Many factors must be considered when methods are being developed for the control of arthropods attacking man and animals. However we could, until recently, hardly look with pride on the progress that had been made in overcoming some of the major obstacles to improved health standards and world economy. It is not generally known, for example, that during and after World War I there were more casualties in Europe due to louse-borne typhus than were caused by the World conflict. Furthermore, at the beginning of World War II we were little better prepared to control lice or typhus epidemics than during World War I.

Fortunately progress during the last 7 or 8 years in controlling arthropods which attack man and animals has been phenomenal. No field of biological science has shown greater progress during the same period of time. It is possible today to break, within a few days or weeks, epidemics of human diseases such as louse-borne typhus, malaria, dengue, sand fly fevers, and a number of other important diseases. Important progress also has been made in the veterinary field of insect control.

The great progress in the field of medical and veterinary entomology can be attributed largely to the discovery and development of a number of highly effective insecticides and repellents as well as methods and equipment for their application. The most important of the new chemical agents for controlling arthropods is the well-known insecticide DDT.

However, the true value of DDT in the future might not be the continued use of this insecticide for controlling arthropods but rather that it has pointed the way for achieving insect control with a degree of efficiency hardly considered possible as late as 10 years ago. There are in fact several new insecticides available today, and others in the early stages of investigation, which in some respects are superior to DDT. Among the newer promising chemicals available for controlling arthropods affecting man and animals are benzene hexachloride, chlordane, toxaphene (chlorinated camphene), methoxychlor, TDE (also called DDD), several synergists for pyrethrum, and various insect repellents.

Along with the development of the highly effective insecticides and their widespread use for the control of insects affecting man and livestock, it should be pointed out that new problems have arisen, the chief one being the question of toxic effects of these materials to man, animals, and wildlife. There is no evidence at present that the widespread use of DDT has caused harmful effects to man and animals. Available toxicological data and the absence of serious toxic reactions resulting from its use suggest that this material, as well as some of the related insecticides, is not likely to result in acute toxicity hazards if employed with reasonable precautions. Likewise, there is no evidence of serious upset of nature's balance of beneficial forms of animal life when DDT is applied over large areas for controlling insects such as mosquitoes.

Although toxicity studies with some of the new chemicals have been pursued rather extensively, toxicologists are concerned about the possible long-range accumulative effects of some of these materials when man or animals are repeatedly exposed to them or

[1] Most of this review deals with first-hand information made available to the writer by several laboratories of the Bureau of Entomology and Plant Quarantine, principally those located at Orlando, Florida, and at Kerrville, Texas. The investigations at Orlando were supported by grants from the Office of Scientific Research and Development during 1942-45, and since that time funds for the research were made available by the National Military Establishment.

when they are consumed in small quantities over a period of years. Most of the new insecticides have gone into use in the medical and veterinary fields without adequate knowledge regarding their acute or chronic toxicity hazards. There is probably no problem in the medical and veterinary entomological fields more urgent than intensified research to study all aspects of the toxicity of known and newly developed insecticides and insect repellents. On the basis of comparative toxicity, most of the newer materials are of a lower order of toxicity than are the arsenicals and some of the other old insecticides which have been employed for many years. However, more extensive use of the new insecticides under almost every conceivable condition permits greater and more varied opportunity for man and animals to become exposed.

The purpose of this paper is to summarize in a general way the recent advances in the control of insects, ticks, and mites which attack man and animals. There have been so many new developments that the writer has not found time to present detailed information regarding them, nor has he found it practical to give credit to the many individual investigators who have been responsible for the rapid progress.

Recent Advances in Medical Entomology

Three methods are generally employed in controlling arthropods attacking man. In a broad sense these methods might be classified as follows: 1) Personal protective measures, 2) premise treatments, and 3) area control measures. All three methods might have to be applied to obtain maximum protection, but this depends on the type of arthropod involved and the circumstances existing in a given area.

Personal protective measures

Recent investigations on the measures to use for personal protection have been principally along two lines—1) research on insect repellents for use on the skin to protect individuals from attack by mosquitoes, black flies, sand flies, and other similar insects, and 2) the development of repellents or toxicants largely for treatment of clothing to protect individuals from attack by human lice, mites, ticks, fleas, and mosquitoes.

Mosquito repellents.—During the recent war, dimethyl phthalate, Indalone (*n*-butyl mesityl oxide oxalate), 2-ethyl hexanediol-1, 3, and a 60-20-20 mixture of these three materials in the order named were developed for the Armed Services as repellents for mosquitoes, black flies, sand flies, and other related insects. Several thousand compounds were tested during and since the war, and a number of other repellents have been developed which are of the same general order of effectiveness as those mentioned. Included among these are dimethyl carbate; N, N,-diethylsuccinamic acid, n-propyl ester; and ethyl beta-phenyl-beta-hydroxy propionate. Repellents vary considerably in their degree of effectiveness, the results depending on the kind and species of insect and the conditions under which the repellents are employed. However, they will usually protect individuals from mosquitoes and black flies for periods of 1 to 4 hours. Considerable effort has been devoted to developing repellents for treatment of clothing to prevent mosquitoes from biting through. The repellents mentioned, expecially Indalone, will provide considerable protection. A number of other materials as effective as or more so than Indalone are now being investigated.

Miticides. — Among the most annoying pests of man in the United States are the small mites (*Eutrombicula spp.*) commonly called chiggers or red bugs. However, in some parts of the world the chigger mites are of greater importance because they are vectors of a rickettsial disease, scrub typhus. Dimethyl phthalate, butyl phthalate, and benzyl benzoate were employed successfully during and immediately after the war by the Allied Armed Forces. Recently, however, several materials have been developed at the Orlando laboratory which are far more persistent than those mentioned. Among the most effective are benzil, diphenyl carbonate, and *p*-cresyl benzoate. These materials impregnated into clothing at the rate of about 2 ounces for the average army uniform will provide complete or nearly complete protection against chiggers

in Florida after the clothing has been laundered four to six times.

Louse and scabies control.—The successful use of DDT for controlling the body louse (*Pediculus humanus corporis* Deg.) during and since the war is well known. DDT at a concentration of 10 per cent was most generally employed. A DDT dust treatment will provide excellent control of body lice as well as head lice (*Pediculus humanus humanus* L.), and is the most practical method of applying the insecticide for this purpose. However, considerable research has been directed toward developing the impregnation method of employing DDT. When the treatment is used in this way, it is much more persistent. When ordinary woolen underwear is treated with solutions or emulsions containing 1.5 to 2 per cent of DDT, the garments will control lice even after they have been laundered four to six times. In case of a national emergency the treatment of underwear before it is issued to the servicemen in combat areas seems to offer possibilities of protecting them from lice during entire campaigns.

Aside from the use of dusts and impregnated garments, DDT has controlled human lice when used in a special liquid preparation known as the NBIN formula. This preparation in the concentrated form contains 68 per cent of benzyl benzoate, 6 per cent of DDT, 12 per cent of benzocaine, and 14 per cent of Tween 80 (an emulsifying agent). When diluted at the rate of 1 part of the concentrate in 5 parts of water and thoroughly applied, the treatment will provide complete control of head lice, body lice, or pubic lice (*Phthirus pubis* (L.)) on individuals. The benzyl benzoate was chosen as the principal solvent for the concentrate so that the formula could also be used for controlling the itch mite (*Sarcoptes scabiei* Deg.). A single thorough treatment with the diluted preparation will eliminate scabies infestations.

Some of the other new insecticides, such as toxaphene, chlordane, and benzene hexachloride, are also highly effective louse-killing agents. Toxaphene, in particular, is superior to DDT when used as a dust or when impregnated in clothing. Chlordane is of about the same order of effectiveness as DDT, whereas benzene hexachloride is highly effective but less persistent than DDT. However, these materials are not recommended for louse control at the present time because of insufficient information relative to their toxicity to man.

Tick repellents and toxicants.—There is increasing interest in the development of treatments that will protect individuals from attack by ticks. These arthropods not only cause discomfort but they transmit several rickettsial and other diseases to man. Considerable progress in developing clothing treatments effective against ticks has been made during recent years. During the war, the results of research at the Orlando laboratory demonstrated that dimethyl phthalate, Indalone, and benzyl benzoate offered considerable protection when applied to clothing. Since the war a number of promising tick repellents or toxicants have been investigated by the Orlando laboratory and by the U. S. Public Health Service. Among the most promising new materials against the lone star tick (*Amblyomma americanum* (L.)) are N-(*n*-butyl) acetanilide: *n*-hexyl ester of mandelic acid; beta-phenyl-beta-hydroxypropionic acid, ethyl ester; and diethylphthalate.

Flea repellents and toxicants.—DDT powders will control fleas when applied to infested individuals. The insecticide kills the fleas rather slowly and therefore considerable effort has been devoted to the development of more desirable treatments for individual protection. Powders containing 10 per cent of DDT and 0.1 to 0.2 per cent of pyrethrins plus 0.5 to 1 per cent of piperonyl butoxide or N-isobutylundecylenamide are at present considered promising treatments. In addition to the development of dust treatments, efforts have been made at the Orlando laboratory to develop clothing treatments which will prevent flea infestations. A number of promising compounds under investigation include benzyl benzoate, phosphoric acid, tributyl ester, and caproic acid 1.5 pentanediol monoester.

PREMISE TREATMENT

The development of highly effective and long-lasting treatments for controlling in-

sects that invade homes and other buildings has, without doubt, represented the greatest single advance in the field of medical entomology. The value of DDT as a residual insecticide for controlling mosquitoes, flies, sand flies, fleas, bedbugs, and other insects is well known. For this reason the discussion of new insecticides will be largely restricted to a summary of the performance of new insecticides other than DDT. However, before proceeding with this summary the subject of insecticide-resistant arthropods will be discussed.

Insecticide-Resistant Arthropods. — Until very recently DDT was employed with phenomenal success in controlling the house fly (*Musca domestica* L.). However, during 1948 numerous reports from the United States and some from other parts of the world have indicated that this insect in certain localities is no longer being controlled with DDT residual sprays. Because of the importance of these failures, the Bureau of Entomology and Plant Quarantine, the New Jersey State Agricultural Experiment Station, the California Agricultural Experiment Station, the U. S. Public Health Service, and a number of commercial concerns dealing in insecticides, initiated intensive investigations to determine the cause. This problem has also been studied in Italy, Switzerland, and other nations. Most, if not all, of the institutions investigating the problem have come to the conclusion that house flies in some areas have developed a marked resistance to DDT.

The magnitude of this resistance can be illustrated by summarizing some of the research conducted at the Orlando laboratory. In 1945 studies were initiated to determine whether house flies were likely to develop DDT-resistant strains. When the flies were subjected to treatments with DDT space sprays, so that only about 5 to 10 per cent of each generation survived to perpetuate the colony, a strain two or three times as resistant to DDT as the parent strain was developed after about 15 generations. This special colony was not only more resistant when DDT was applied as a space spray but also when it was exposed to DDT residual treatments. As the selection continued through subsequent generations, the colony became more and more resistant to DDT. To obtain equal kill of the nonresistant and resistant strains during the 55th to 60th generations, the concentration required for the resistant strains was over 100 times that required for the nonresistant strain. When measured from the standpoint of immunity to residual deposits, the exposure time for approximately 100 per cent kill of the resistant strain was 16 hours or longer (approximately 1,000 minutes) as compared with approximately 5 minutes for the flies from the parent nonresistant stock.

When reports of DDT failures were received during 1948, wild house flies were collected from several states around dairies where DDT has been used for 2 to 3 years. Tests with these flies have shown that certain strains require from 30 to 40 times the period of contact with DDT-treated surfaces to produce the same percentage mortality obtained with laboratory strains of house flies that have not been exposed to DDT.

It is doubtful whether anyone expected such magnitude of resistance to develop among house flies within 2 or 3 years. This problem is considered a highly significant adverse development in the medical entomology field. Reports of DDT-resistant bedbugs (*Cimex lectularius* (L.)) have also been received; however, carefully controlled research has not been conducted to confirm them. There are no indications of DDT-resistant strains of *Anopheles* mosquitoes, but there is no reason to doubt that such strains might develop among some of the hundreds of species which occur throughout the world.

The dramatic occurrence of insecticide-resistant house flies and the possibility that other species might develop such resistance should serve to emphasize the need for continued research in the field of medical and veterinary entomology, even though effective materials and methods of controlling various species might be currently available.

Performance of New Insecticides—Benzene hexachloride.—The insecticidal and acaracidal value of benzene hexachloride was discovered in France and Great Britain, but much of the research during recent years has been done in the United States.

The gamma isomer of benzene hexachloride is among the most active of the new insecticides against insects, ticks, and mites. However, its rather high degree of toxicity to higher animals and its musty odor are factors which tend to limit the widespread use of this material for controlling some of the species.

Against flies and mosquitoes gamma-benzene hexachloride employed as a space spray is considered more effective than DDT, but the residual action of this insecticide is generally less persistent than that of DDT. DDT-resistant strains of house flies, already discussed, show relatively little resistance to benzene hexachloride. Investigators at the California Agricultural Experiment Station at Riverside have reported satisfactory control of house flies for several weeks with benzene hexachloride in dairy barns where DDT has failed.

Chlordane.—Chlordane, discovered by the insecticide industry in the United States, is also effective against a wide variety of insects which invade homes. It has been widely used with outstanding success for the control of such insects as cockroaches and ants. When used as a space spray, chlordane is somewhat more effective than DDT against house flies, but is less so when employed against adult mosquitoes. Although residual treatments of chlordane are normally less persistent than DDT against house flies and mosquitoes, chlordane is more effective than DDT against DDT-resistant house flies. Chlordane is therefore a promising treatment for fly control. However, further study is necessary under a wide range of conditions and against various strains of house flies before its true value for this purpose can be determined.

Methoxychlor.—The methoxy analog of DDT, known as methoxychlor, approaches DDT in effectiveness when used as a space spray or a residual spray against house flies. However, it was given little consideration for practical application because it costs more and proved considerably less effective than DDT against mosquitoes and certain other insects of medical importance. Recently, however, it has shown considerable promise as a control for DDT-resistant house flies. In laboratory studies these flies have shown considerably greater tolerance to methoxychlor than normal strains but not to the same extent as to DDT. The insecticide is suggested as a trial substitute under conditions where DDT has failed. However, as with chlordane, more study under various conditions is needed before the true value of methoxychlor in controlling house flies can be determined. When compared with DDT and other chlorinated hydrocarbons now available, methoxychlor is considered much less toxic to warm-blooded animals.

Piperonyl butoxide.—Piperonyl butoxide is the best known and most generally effective of an interesting group of compounds which increase the insecticidal activity of pyrethrum. When employed in proper proportions, piperonyl butoxide will increase the toxicity of pyrethrum to house flies approximately 10 times. It is therefore being used extensively in space sprays and aerosols.

Piperonyl butoxide also increases the activity and prolongs the action of pyrethrum, when the combination is used as a residual spray for certain insects which invade buildings. N-Propylisome is another new synergist for pyrethrum which is coming into widespread use.

AREA CONTROL MEASURES

The most spectacular advance in the field of medical entomology has been the development of DDT during the war for controlling mosquitoes, both adults and larvae, when applied in small amounts as sprays or aerosols. Although no outstanding new insecticides have been developed since then, there has been steady progress in the development of more efficient equipment for applying DDT from aircraft and of several new types of ground equipment for producing sprays and aerosols (fogs). DDT is now being used extensively in amounts ranging from 0.05 to 0.25 pound per acre for controlling adults and larvae of various species.

Perhaps the outstanding new advance in area control of arthropods has been the work on black flies (Simuliidae), mites, and ticks. Several new insecticides and acaracides have been investigated in connection with the control of these parasites.

Black Flies.—As a result of some early preliminary investigations in South and Central America by the Rockefeller Foundation, it was known that DDT offered considerable promise for the control of black fly larvae breeding in streams. Investigations of the various new insecticides for controlling black flies in North America were not initiated until about 1947. However, during 1947 and 1948 the United States Bureau of Entomology and Plant Quarantine, the National Military Establishment, and the Canadian Department of Entomology have conducted extensive investigations on the control of black flies. These studies have shown that black fly larvae can be controlled with minute amounts of DDT applied to infested streams.

In Alaska oil solutions of DDT applied from the air at the rate of 0.1 pound of DDT per acre to 800-foot sections of streams controlled black fly larvae for at least 2 to 3 miles down stream.

The Canadian workers have recently reported that black fly larvae breeding in large streams were controlled for a hundred miles or more when DDT was applied. The Bureau of Entomology and Plant Quarantine demonstrated that DDT applied for gypsy moth control completely eliminated black fly larvae in streams in an area of fifty thousand acres. Thus far DDT has not been employed in practical control operations. Studies are underway by the Fish and Wildlife Service, in cooperation with several agencies, to determine whether such control procedures will have any serious effects on fish. The minimum amount of DDT needed to control black fly larvae is far below the toxic level for fish, but further studies should be made to determine the effects of the treatment on aquatic insects and other fish foods.

Investigations in New Hampshire by the Orlando laboratory have shown that TDE is more effective than DDT for controlling black fly larvae. It is also less toxic than DDT to certain fish and may therefore be more useful than DDT for black fly control.

Considerable success in controlling black fly adults in the New England States by means of DDT aerosols has been achieved by workers of the New York State Agricultural Experiment Station. However, the cooperating agencies mentioned in connection with the studies on black fly larvae failed to demonstrate satisfactory control of black fly adults in Alaska and Canada when DDT was applied as sprays or aerosols, because of rapid migration of the insects into treated areas from surrounding untreated areas.

Chiggers and Ticks.—Workers at the Orlando, Florida, and Savannah, Georgia, laboratories of the Bureau of Entomology and Plant Quarantine have shown that chigger mites (*Eutrombicula* spp.) can be effectively controlled in their natural habitats with dusts or sprays of some of the new insecticides. Benzene hexachloride, chlordane, and toxaphene applied at the rate of 2 pounds per acre will provide excellent control. These insecticides, as well as DDT, are also highly effective in controlling ticks, particularly the lone star tick. The New York Agricultural Experiment Station and the Bureau of Entomology and Plant Quarantine have also demonstrated effective control of the American dog tick (*Dermacentor variabilis* (Say)) with DDT applied at the rate of 1 pound per acre.

Mosquitoes.—A number of the newer insecticides have been investigated as mosquito larvicides and adulticides by agencies such as the U. S. Public Health Service, the Bureau of Entomology and Plant Quarantine, the Tennessee Valley Authority, and a number of State mosquito-abatement organizations. None of the compounds has proved as effective as DDT in controlling adult mosquitoes when applied under outdoor conditions. However, as a mosquito larvicide, TDE is equal to and in some cases superior to DDT.

Parathion is highly effective against mosquito larvae and adults. It is so highly toxic to warm-blooded animals, however, that it is questionable whether it can be used for mosquito control.

Recent Advances in Veterinary Entomology

Time and space will not permit a thorough review of recent research in the field of veterinary entomology. However, as in the field of medical entomology, great prog-

ress has been made. The advances have for the most part been due to the high degree of effectiveness of some of the new insecticides for controlling several important livestock pests. The most important of the new insecticides for controlling animal parasites is DDT. However, the performance of this insecticide in the livestock-pest field is well known, and it will be mentioned only as a standard of comparison in reviewing the results reported with the newer chemicals.

This discussion will touch only incidentally on the important toxicological problem. However, as in the field of medical entomology, the widespread use of some of the newer insecticides for controlling livestock insects has raised important questions relative to the hazards of their use, not only to the livestock but also to the consumers of animal products from treated animals. Following the discussion of the new insecticides, a brief review will be given of some recent and interesting work in the field of internal medication for controlling external animal parasites.

NEW INSECTICIDES FOR CONTROLLING LIVESTOCK INSECTS

Benzene hexachloride. Benzene hexachloride is effective in controlling a number of parasites of livestock. All the species of lice attacking livestock are highly susceptible to this insecticide. It is not only effective against the motile forms but it also possesses some ovicidal properties. A spray containing 0.25 to 0.5 per cent of technical benzene hexachloride (10-12 per cent of the gamma isomer), or 0.25 to 0.05 per cent of the gamma isomer, will provide satisfactory control of both *Anoplura* and *Mallophaga* on cattle. The technical grade is at least as effective and possibly more effective than DDT at the same concentrations. The insecticide is also highly effective against all stages of several species of ticks attacking livestock in this country. Concentrations as low as 0.25 per cent of the technical material (0.025 per cent gamma) will kill engorged forms of the lone star tick and the winter tick (*Dermacentor albipictus* (Pack.)). A concentration of 1.5 per cent or even higher percentages of DDT are required to kill engorged forms of these species. However, benzene hexachloride has less persistence than DDT and some of the other new materials, and animals are subject to reinfestation within a short time after treatment.

Benzene hexachloride is also highly effective in controlling the sheep tick (*Melophagus ovinus* (L.)) and is superior to DDT. However, rotenone, which has been used extensively for the control of the sheep tick, is also highly effective and from the standpoint of economy and safety is perhaps the best all-round treatment for this parasite.

Benzene hexachloride, according to investigations by the Bureau of Animal Industry, various livestock associations, State experiment stations, and industrial concerns, is highly effective for controlling the mange mite and other mites on swine, cattle, and sheep.

The acute toxicity of benzene hexachloride to livestock is rather high, since it has been shown that young calves less than 3 months old may show toxic symptoms when thoroughly treated with sprays containing 0.05 per cent of the gamma isomer. However, yearlings or older cattle have shown no toxic reactions when treated repeatedly with concentrations of 0.15 per cent to 0.2 per cent of the gamma isomer. The musty odor of benzene hexachloride is also objectionable, and there has been some concern over possible tainting of flesh or milk of animals treated with this insecticide. However, there has been no clean-cut evidence that tainting has occurred when the insecticide has been employed in actual practice.

Chlordane.—Chlordane in general is comparable with DDT against various livestock pests, such as all species of lice attacking cattle, sheep, goats, and swine. It is distinctly more effective than DDT against the sheep tick. It is also more effective than DDT against engorged forms of the lone star tick and the winter tick. Concentrations of 0.5 to 0.75 per cent will destroy all stages, whereas 1.5 per cent or more of DDT is required to kill engorged adults. The protection against reinfestation offered by chlordane against the lone star tick is comparable with that of DDT, whereas against the winter tick chlordane is superior to DDT.

For control of the horn fly (*Siphona irritans* (L.)) chlordane is somewhat less effective than DDT, although good control can be obtained when it is applied in the amounts generally used for DDT.

Although chlordane has been used rather extensively in certain areas for controlling livestock pests, apparently without harmful effects, the insecticide is known to produce toxic effects when sprays containing 1.5 to 2 per cent are thoroughly applied at frequent intervals to cattle, sheep, and goats. For this reason further toxicological study employing minimum concentrations needed to control certain parasites should be conducted to determine whether the insecticide can be employed without harmful effects to the host.

Toxaphene.—Toxaphene in general is at least comparable with DDT and chlordane for controlling the various species of lice attacking farm animals. It is also one of the most promising of the new materials for the control of various ticks attacking livestock. For these parasites the insecticide appears to be at least equal to chlordane and generally superior to DDT.

For horn fly control toxaphene is somewhat slower in action but of the same general order of effectiveness as DDT. For sheep ticks it is more effective than DDT but less effective than chlordane or benzene hexachloride.

The reason for delay in recommending the use of toxaphene as a general-purpose insecticide for controlling insects and ticks attacking livestock is the lack of information regarding its toxic effects to animals. In practical control operations some cattle, principally calves, have died after being dipped in toxaphene dips containing 0.55 per cent of the insecticide. It has been fairly well established that the deaths occurred largely because the emulsion formulations had decomposed before they were used, and as a result the dip was improperly mixed. Controlled toxicological tests have shown that the sprays or dips containing from 1.0 to 1.5 per cent concentrations of toxaphene might prove toxic to young calves. However, cattle a year or more of age have been treated repeatedly with 1.5 to 2 per cent concentrations without apparent toxic effects.

It is possible that toxaphene properly formulated and carefully mixed and applied can be used with safety on livestock. However, further studies on various aspects of the toxicology of this insecticide must be undertaken before its potential use for the control of livestock pests can be determined.

Piperonyl butoxide.—Piperonyl butoxide, discussed in connection with the control of certain insects affecting man, is also being employed in combination with pyrethrum for controlling certain livestock pests. This combination will provide satisfactory control of lice on cattle when applied at a concentration as low as 0.005 per cent of pyrethrins and 0.05 per cent of piperonyl butoxide. It also offers promise for the control of flies attacking livestock. The chief advantage offered by pyrethrum is its low toxicity to higher animals. According to investigations by the Food and Drug Administration, piperonyl butoxide is also of a very low order of toxicity to higher animals.

Methoxychlor.—Methoxychlor is the least toxic to higher animals of the various new chlorinated hydrocarbon insecticides. It is an effective insecticide for controlling horn flies and lice on cattle and is only slightly less effective than DDT against the former and about equal to DDT against the latter. The widespread use of DDT on dairy cattle and the appearance of small amounts of this insecticide in the milk following its use is creating some concern among toxicologists. No significant amounts of methoxychlor have been demonstrated in milk of dairy animals following its use as a 0.5 per cent spray. This observation, together with its inherent lower toxicity, makes methoxychlor of special interest for controlling insects affecting dairy animals. The material is somewhat more costly than DDT or some of the other insecticides.

TDE.—TDE is of about the same order of effectiveness as methoxychlor against horn flies and lice on cattle. According to the Food and Drug Administration, the degree of toxicity of TDE to warm-blooded animals is intermediate between that of DDT and methoxychlor. Investigations by the Bureau of Entomology and Plant Quarantine have shown that the amount of in-

secticide appearing in the milk of dairy animals treated for horn fly control is somewhat less than the amount following the use of DDT. The average for DDT during a season's schedule of spray-treatment for horn fly was about 0.6 to 0.7 part per million, whereas the average for TDE was about 0.4 part per million.

CHEMOTHERAPEUTIC AGENTS FOR CONTROLLING ARTHROPOD PARASITES OF ANIMALS

The possibility of controlling arthropod parasites of animals following the feeding or injection of chemicals has been considered by entomologists and parasitologists for many years. Until recently no material was known which would control any of the parasites attacking animals. However, during the last few years several investigators have demonstrated that certain blood-sucking external parasites can be destroyed by administering chemicals to the host. Investigators at the Orlando laboratory first demonstrated that bedbugs were killed when they were permitted to take blood from rabbits given large doses of DDT or pyrethrum. Subsequent research demonstrated that human body lice, which fed on rabbits, were killed when 2-pivalyl-1,3-indandione in single doses as low as 2.5 mg. per kilogram of body weight was administered orally or injected into the host. Although these doses might have caused toxic reactions, no gross symptoms of toxicity were noted. This same material has controlled sucking lice on swine and dogs when administered at the rate of 5 to 10 mg. per kilogram of body weight (unpublished data obtained by the Kerrville, Texas, and Corvallis, Oregon, laboratories of the Bureau of Entomology and Plant Quarantine).

British investigators have shown that bedbugs (*Cimex* spp.), yellow-fever mosquitoes (*Aedes aegypti* (L.)), and certain ticks were killed when fed on rabbits given benzene hexachloride. Other investigators in Hungary have recently reported controlling mites and lice on animals by oral administration of chemicals to the host.

Investigations in the field of chemotherapy have by no means progressed to a stage where chemical agents can be administered internally for the control of external parasites. Chemicals such as benzene hexachloride and 2-pivalyl-1,3-indandione are quite toxic to animals. However, in some cases the amounts producing insecticidal action in the blood of the host are at least below the dose producing gross toxic symptoms. This approach for controlling animal parasites warrants further exploration.

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COMMUNICATION TO THE EDITOR

Stockbridge, Massachusetts

April 13, 1949

Dear Doctor Adler:

Dr. Mahlon Ashford, Editor of the Bulletin of the New York Academy of Medicine has sent me your letter to him of April 8 in which you effectively contradict a statement I made in my article, "A Critique of the Present Status of the Psychotherapies" in the February (1949) issue of the Bulletin.

My statement, which appeared on page 111 of this issue, was "This (Adler's Individual) psychology and system of therapy died out with its leader." You point out that there are three institutes of Individual Psychology in the United States—New York, Chicago, and Los Angeles—and that there are a number of other evidences in this country and Europe that Individual Psychology is quite alive. Obviously I was mistaken on this point. I gladly retract the statement and extend my apologies. Also I have requested Doctor Ashford to publish my retraction.

Sincerely yours,

ROBERT P. KNIGHT, M.D.

RPK/hh

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ANNOUNCEMENT

Due to the rise in the cost of printing and paper, The New York Academy of Medicine finds it necessary to increase the subscription rate for THE BULLETIN, effective 1 August 1949 to $5.00 a year for subscribers in the United States, Canada and Cuba.

THE EDITOR